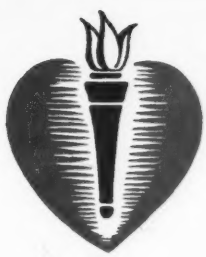
MARCH 1958
VOL. XVII NO. 3

Circulation

FICIAL JOURNAL of the AMERICAN HEART ASSOCIATION



31st Scientific Sessions of the American Heart Association
San Francisco, Calif., from October 24-26, 1958
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1. Briller, S. A.: *M. Clin. North America* 41:619, May, 1957.
2. Tainter, M. L.: *Bol. Asoc. méd. Puerto Rico* 47:305, Aug., 1955.

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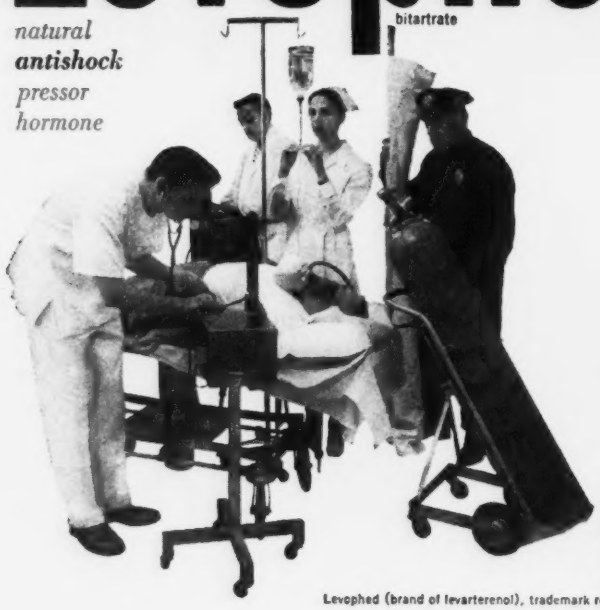

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OFFICIAL JOURNAL of the AMERICAN HEART ASSOCIATION

Editorial

Epidemiology and Coronary Heart Disease

CLINICIANS are concerned with patients, epidemiologists with populations: in studying disease, epidemiology is concerned with its frequency in populations. Populations or groups may be characterized by their mode of life and epidemiology can thus study the frequency of disease in relation to this, comparing the frequency under different ways of living. For example, the number of deaths from cholera in households taking water from this supply and from that is compared, or of cases of pellagra among those eating one diet and of others with different food habits. Epidemiology is the main method of identifying connections between ways of living, the environment, and health and disease. There is mounting evidence that atherosclerosis and its principal complication coronary (ischemic) heart disease are related to the mode of life, and there is growing interest therefore in the possible contributions epidemiology might make in unraveling the many problems involved.

There are several types of epidemiologic study, and I will illustrate briefly from 3. First, the *vital statistics* of populations; second, *large-scale surveys* of populations and groups in which it is usually practicable to collect only a few facts about the many people involved; third, studies of *small samples* in which it may be possible to learn a great deal about all of the few persons being investigated. These 3 technics overlap of course and in actual research they and others are often combined in some way.

Vital Statistics

Of considerable interest today are the attempts to compare mortality from coronary heart disease in different countries. Information is available also on a population basis about the consumption or availability of various nutrients, and the popular exercise is to relate certified mortality from coronary disease to these national averages of total fats, or animal fats, or hardened fats, etc. Straightaway it may be said that too much weight is at present being placed on these statistics, and the possibility must be faced that they are individually and severally leading us up the garden path. Some promising generalizations have been drawn. On the other hand there are various awkward facts that proponents of single or simple dietary hypotheses about coronary heart disease must dispose of. To take one example, western, highly developed countries, with high living standards, high fat diets, high serum cholesterol, good medical services—and vital statistics—seem all to have greater mortality from coronary heart disease than poorer countries with less fat consumption, inferior medical services, etc. The rest is confusion. Among the dozen or so western countries that can reasonably be compared in this way there is little if any relationship between fat consumption and mortality rates. Holland (moderately high total fat consumption), Norway (high), and Denmark (very high) all have sizable but comparatively low coronary mortality rates; in contrast, Finland (moderately high fats), Scotland (high), and New Zealand (very high) all register severe mortality from coronary heart disease in middle-aged men.[1]

The kind of question that these geographic exercises raise is whether there is a

"threshold" of fat consumption above which coronary heart disease becomes common; and if what happens over the threshold to determine the particular level of a country's coronary mortality depends on other factors —on multiple causes. Such a threshold might be at a "moderately high" daily level of 100 or 110 Gm. of fat per person, figures that may be compared with the "very high" average consumption of 140 to 150 Gm. in Denmark, New Zealand, and the U. S. A. But this threshold may be less than 100 Gm., that is if it exists at all. The chief limitation to the use of population statistics is that the countries with lower average consumption than, say, 100 or 110 Gm. of fat per day tend to be the poorer countries, and to have less reliable statistics, e.g., by cause of death, than those with higher nutritional standards. And, quite apart from this consideration, the possibility that international differences may be largely or partly due to interracial differences, i.e., to genetic causes, is only now beginning to be faced with the studies of similar racial groups who happen to be living in different environments.

Large-Scale Surveys

Other problems arise as soon as observation of human behavior is attempted instead of the manipulation of existing statistics; and often this is started in the hope of elucidating the statistics. The epidemiologic method is concerned with all the persons in the group being studied. Otherwise, the rates whose production is the essence of the method cannot be calculated. In its simplest form the method may be stated as follows: in one group there are 1,000 men x of whom suffer from angina of effort, and all the rest do not. This experience (an angina rate of x per 1,000) can be compared with that of another 1,000 men among whom there are y cases of angina, the remainder of the 1,000 being free of this symptom (an angina rate of y per 1,000). The total number in the group needs to be known for the denominator of the rate, and every individual in the group must be accounted for to provide an accurate figure to put into the numerator. In practice, therefore, when studying large groups it is usually possible to get only very few facts about all the individuals in them. Thus, in the studies by our Unit and their own industrial physicians of 25,000 London transport workers, now continuing over 9 years, we are able to do little more than ascertain the frequency of disabling illness due to coronary heart disease (a few suffer it and the great many do not) and the frequency of death from this cause in several occupations, due adjustment being made for age. Latterly the "shape" of the busmen has also been introduced into the analysis insofar as this can be inferred from the uniform worn. A suggestion arising from these studies is that one group of men, the bus drivers, has substantially more "sudden death" and rapidly fatal coronary heart disease than another group in the same social circumstances, the conductors of these double-decker vehicles. From such a difference (it was found also when government clerks and minor officials were compared with postmen) several hypotheses can be formulated; the one we adopted is that physical exercise at work is protective against coronary heart disease—bus conductors frequently go up and down the stairs, bus driving is a "sedentary" job. The hypothesis is now being subjected to multiple tests, including clinical studies of samples of working busmen and a national postmortem survey. This survey has shown a greater prevalence of ischemic myocardial scars, especially the large solitary ones, among "light" workers dying of cancer, etc., than among "heavy" workers of the same age so dying; and there is indication also that hypertension is commoner in light workers. Comparison of the coronary arteries, by type of occupation, for occlusive and nonocclusive atherosclerosis is now under way.

There is much scope for these large-scale surveys. The various studies of American and British men, classified by a few simple facts on their smoking habits, have produced such discrepant findings that, at the least, the existence of any *direct* relationship be-

ween smoking and coronary heart disease of iddle age becomes problematic. At present is urgent to devise simple technics for esti- ating the composition of individual diets so at the subsequent clinical history of several ousand eaters of excess calories, for ex- mple, or big fat eaters, can be compared ith that of other thousands of men sim- arly situated but, say, abstainers or eating latively little fat. (If such a technic were vailable, it would of course also be used in n attempt to get answers from comparison f clinical coronary cases and such controls s could be designated.) However, even in he well-established field of electrocardiogra- phy the methodologic problems of taking and eading mass electrocardiograms have by no means been solved. Meanwhile, there is a great need to develop simple prevalence stud- ies in various communities, using the best method and indicators currently available, to learn about the dimensions of coronary heart disease and the "naturally" occurring varia- tions by locality, occupation, social status, and so on. Perhaps the existing Notification machine of the Health Officer may be appli- cable to this, today's most urgent problem in Public Health. There is room for much local and comparative experiment in tackling this kind of problem.

Sample Studies

The intensive study of small samples—at home say—of heavy workers and light, or high pressure executives and routine clerks, and abroad of Guatemalan city dwellers and peasants, or Cape Europeans and Ban- tus—is self-explanatory and now provides the most comfortable meeting ground between epidemiologists and clinicians. If the sam- pling is good, much can be learned about even large populations from study of a small number of individuals in them. With bigger resources it is possible to study bigger num- bers—but it is a fallacy that multiplication of subjects, examiners, and examinations in- troduces merely *quantitative* changes into an investigation. Each type of study has its own virtues as well as limitations. The great achievement of small sample studies has been to demonstrate the range of "normal" blood lipid values by cross-cultural, as the anthro- pologists would say, surveys and to raise the question of what is in fact a normal or healthy level. These international collabo- rative investigations are among the most ex- citing developments of modern medicine.[2] They are so expensive, however, that it is essential to assure that the maximum is ex- tracted from them. At present there are few studies of *comparable* groups in "developed" and "underdeveloped" countries — for ex- ample, manual workers of Cleveland and Calcutta—or for that matter in highly de- veloped ones—clerks, say, in Copenhagen and Auckland—in terms of nutrition, blood lipids, clinical history, electrocardiographic pattern, and so on, i.e., studies that attempt a real-life correlation in satisfactory samples of the main variables now thought to be relevant. There are already many clues to fol- low in sample studies or in studies of the whole of small population groups[3] from the laboratories, from vital statistics, and from the large-scale surveys. In turn such small- scale studies have already shown that they can feed back hypotheses for testing by other methods of research. The main methods of medical research, clinical observation, lab- oratory experiment, and population survey are complementary.[4-6]

Multiple Causes

It is a clinical commonplace that there are multiple causes of disease. For example, sub- acute bacterial endocarditis is "caused" by (1) the *Streptococcus viridans,* liberated often by (2) surgical procedures, in the pres- ence of (3) a damaged valve—3 "causes" at least of the occurrence of a case of subacute bacterial endocarditis. Or subarachnoid hem- orrhage may be caused by the rupture of a berry aneurysm from a congenital defect in an artery with, often, degeneration in the local lesion, and in the presence of hypertension[7] — several causes again. This elementary principle applies throughout med- icine and as much to disease at the popula-

tion level as at the clinical; but it tends to be forgotten. Thus there *may* be a sole or rather *crucial* cause of coronary heart disease; but in the absence of any evidence of such, experience suggests that it is unwise to assume so. The decline of mortality in Norway during the German occupation is usually and sometimes casually ascribed to the fall in fat consumption during those years. An epidemiologic picture of this problem in public health (it should so be regarded) straightaway warns against any such simplification. There is good reason to suppose that such decline of coronary heart disease as there was, some 20 or 25 per cent possibly, began *before* fat restriction was at all serious. The decline of coronary heart disease was rather less than the decline in cardiovascular disease in young people. There was a fall in the frequency of a large number of diseases in Norway during the occupation—from schizophrenia to cancer of the breast. Moreover, several other factors that might well be related to coronary heart disease were also being affected in a favorable direction in those years: e.g., available calories, average body weight, blood pressure levels, cigarette smoking, physical exercise, maybe even mental health as well. It is not merely academic to ask whether there are multiple causes of coronary heart disease. In the long journey from atheromatous flecking of a coronary artery to the fatal case of coronary heart disease several distinct causes may be operating, and some may be more controllable than others: it may turn out to be more practicable to try to prevent massive thrombosis in atherosclerotic coronary arteries for example, or to promote collateral circulation, than to abolish atherosclerosis.

The prospects for epidemiologic research in coronary heart disease are bright. There has been some successful experience, and with the new interest in this approach in various countries there is every reason to hope for further advance. Several conditions however, will have to be fulfilled if present optimism is to be realized. The most important might be summed up in the necessity for collaboration between laboratory scientists, clinicians who know about heart disease and public health people, epidemiologists and the like who know about field surveys and population studies.

J. N. Morris

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Intravenous Drug Therapy of Stokes-Adams Disease

Effects of Sympathomimetic Amines on Ventricular Rhythmicity and Atrioventricular Conduction

By PAUL M. ZOLL, M.D., ARTHUR J. LINENTHAL, M.D., WILLIAM GIBSON, M.D., MILTON H. PAUL, M.D., AND LEONA R. NORMAN, M.D.

In the treatment of Stokes-Adams disease emergency resuscitation from cardiac arrest can be effected by external electric stimulation or countershock. For the acute problems of persistent ventricular standstill and frequently recurrent seizures, which often appear immediately after resuscitation, intrinsic ventricular pacemakers must be aroused, accelerated, and maintained. In the treatment of these problems the effects of drugs on ventricular rhythmicity and atrioventricular conduction were evaluated. We have found the slow intravenous administration of dilute solutions of sympathomimetic amines to be an effective and safe technic. Epinephrine and isoproterenol were the most useful agents and were comparable in efficacy and toxicity.

EPINEPHRINE and many similar drugs are widely used in the treatment of serious cardiovascular disturbances. In this paper detailed information obtained in the treatment of patients with Stokes-Adams disease is presented concerning the cardiovascular actions of these drugs, especially their effects on ventricular rhythmicity. Thereby, it is hoped, the choice and use of a particular drug for a particular purpose will be improved.

Because the ventricles beat in response to the sinoatrial pacemaker during normal sinus rhythm, the effects of drugs on the slower ventricular pacemakers are masked, except when ventricular arrhythmias are excited. To observe the effects of drugs on ventricular activity in man independent of the sinoatrial pacemaker, Gilchrist[1] and later Nathanson and Miller[2] studied patients with complete heart block. Nathanson[3] also produced transient sinoatrial arrest or atrioventricular block by pressure on the carotid sinus, and during these brief periods he studied the effects of drugs on ventricular rhythmicity. Although valuable, the data provided by these studies are insufficient for the optimal therapeutic use of sympathomimetic drugs.

TECHNIC

During the treatment of 94 patients with Stokes-Adams disease with the new technics of external electric stimulation and defibrillation of the heart,[4-6] opportunities arose in 21 patients to study sympathomimetic drugs and 1-molar sodium lactate[7] under the unique circumstance of complete absence of spontaneous ventricular activity. With electric currents applied externally to the chest wall, emergency resuscitation can be effected from Stokes-Adams attacks due either to ventricular standstill, tachycardia, or fibrillation.* At times, after resuscitation, the heart fails to beat spontaneously when the external pacemaker is turned off. Continuous electric stimulation then is necessary as long as spontaneous ventricular beats remain absent.

In the treatment of this difficult problem, sympathomimetic agents and sodium lactate were administered by intravenous infusion to arouse spontaneous ventricular beats. The arousal of ventricular pacemakers provided an unusual and particularly valuable criterion for the evaluation of the effects of drugs on ventricular rhythmicity. Arousal, being an all-or-none phenomenon, was unequivocal and simpler to evaluate than acceleration and maintenance.

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This investigation was aided by research grants from the National Heart Institute, U. S. Public Health Service (H-2208), and from the Massachusetts Heart Association.

*Cardiac Pacemaker and External Defibrillator manufactured by the Electrodyne Co., Norwood, Mass.

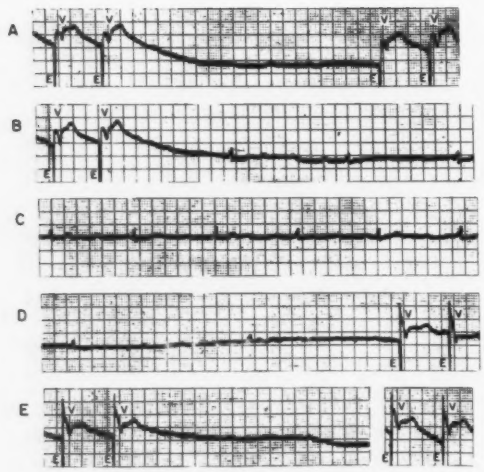


FIG. 1. Electrocardiograms (lead aV_F at half standardization) illustrating arousal of an intrinsic ventricular pacemaker by epinephrine in a patient (E.S.) with prolonged ventricular standstill. *A.* (10:36 a.m.) Electric stimuli (E) produced ventricular responses (V). When no stimuli were applied, there were no spontaneous ventricular beats. *B.* (11:01 a.m.) When stimulation was interrupted after the infusion of epinephrine for 5 minutes, intrinsic ventricular beats appeared. *C.* (11:05 a.m.) With continued infusion of epinephrine the sinoatrial and ventricular pacemakers accelerated; thereupon the infusion was stopped. *D.* (12:27 p.m.) When the idioventricular rate became very slow, syncope occurred and electric stimulation was resumed. *E.* (12:29 p.m.) Intrinsic ventricular beats failed to appear during a test interruption of stimulation lasting 16 seconds; 12 seconds of ventricular standstill between the 2 segments are not shown.

Sympathomimetic drugs and sodium lactate were also administered intravenously to a few patients with intrinsic ventricular activity to prevent recurrent Stokes-Adams attacks by accelerating idioventricular pacemakers, by preventing their disappearance, or by improving atrioventricular conduction.

Blood pressures, electrocardiograms, and rates of drug administration were recorded as often as at 1-minute intervals during periods of change. The P-P and R-R intervals were measured as indices of the sinoatrial and idioventricular rates; variations in QRS configuration indicated changes in ventricular pacemakers, and the relations between P and QRS indicated the state of atrioventricular conduction. Representative values from quantitative data are shown in the figures.

Periods of electric stimulation are shown in the figures by the gray background. Persistent absence of intrinsic ventricular pacemakers was documented in every instance by the absence of spontaneous ventricular beats both during stimulation and during frequent, short test interruptions of stimulation (fig. 1*A*). The absence of intrinsic ventricular pacemakers was observed for hours or days before drugs were administered.

Sympathomimetic drugs were given by intravenous infusion at carefully regulated rates and the state of intrinsic ventricular activity was observed electrocardiographically during test interruptions of stimulation, usually at 1- or 2-minute intervals. Freshly prepared solutions were usually administered at initial rates of 4 μg. per minute (1 ml. or 15 drops of a 1:250,000 solution). The rate of drug infusion was increased stepwise until intrinsic ventricular pacemakers appeared (fig. 1*B*) or until toxic effects were observed, such as premature beats, excessive ventricular acceleration, excessive elevation of the blood pressure, or excessive cerebral stimulation. Then, drug administration was maintained, slowed, or stopped and the cardiovascular effects were noted. If ventricular pacemakers disappeared or became too slow to maintain an adequate circulation, electric stimulation was resumed immediately. If intrinsic ventricular pacemakers again remained absent, further trials of the same drug or other drugs were carried out. In this way repeated quantitative comparisons were made within a short period of time from the same baseline of absent spontaneous ventricular activity.

The effects of 1-molar sodium lactate on ventricular rhythmicity were also studied. It was administered intravenously in amounts ranging from 70 to 200 ml. at rates of 7 to 30 ml. per minute—dosages suggested by Bellet and Wasserman.[7]

RESULTS

The effect of various drugs on ventricular rhythmicity and atrioventricular conduction were studied in 21 patients with Stokes-Adams disease; a total of 83 drug trials was carried out. In 16 patients drugs were administered during 23 periods of absent intrinsic ventricular activity lasting from 2½ to 108 hours during which the external stimulator was the only ventricular pacemaker. In 9 patients drugs were administered on 12 occasions when an intrinsic ventricular pacemaker was already present. The periods of observation lasted 1 to 23 hours; from 1 to 7 drug trials were carried out in each. Epinephrine was tested 37 times; isoproterenol (isopropyl-

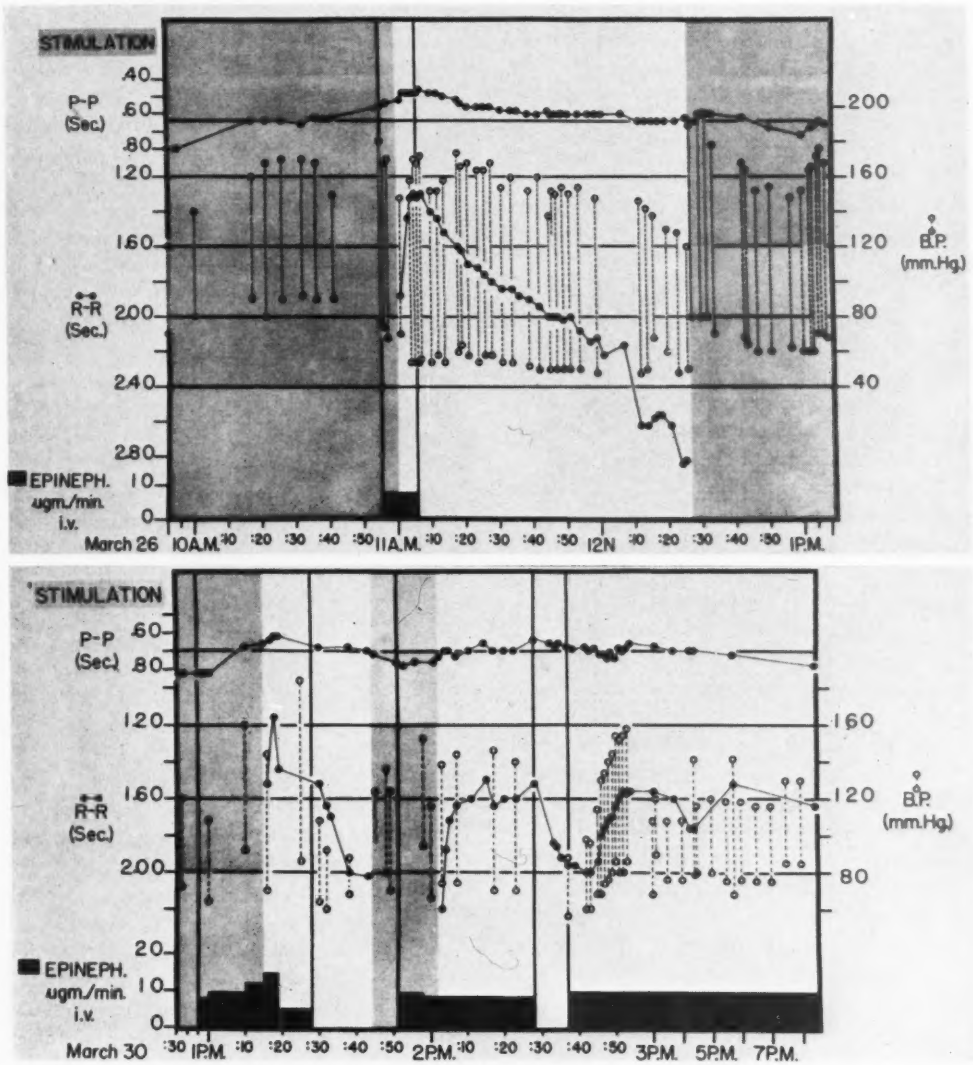


FIG. 2 *Top.* Quantitative data from epinephrine trial illustrated in figure 1. The gray background here and in subsequent figures indicates periods of external electric stimulation when there was no spontaneous ventricular activity.

FIG. 3 *Bottom.* Repeated arousal, acceleration, and maintenance of an idioventricular pacemaker by epinephrine. Arousal of an idioventricular pacemaker at 1:16 and 2:03 p.m. permitted stopping of external electric stimulation (gray background). With excessive acceleration at 1:18 p.m. to a cycle length of 1.16 seconds (53 beats per minute) the drug dose was reduced and the rate slowed. Omission of epinephrine at 1:28 and 2:28 p.m. was followed by excessive ventricular slowing, so that resumption of electric stimulation was necessary at 1:45 p.m. and readministration of epinephrine at 2:38 p.m. Thereafter the ventricular rate was maintained at its former level of 1.60 seconds (38 beats per minute).

norepinephrine or Isuprel*) 29 times; levarterenol (norepinephrine) 10 times; phenylephrine (Neosynephrine) 1 time; and 1-molar sodium lactate 5 times.

Arousal, Acceleration, and Maintenance of Intrinsic Ventricular Pacemakers

Attempts were made to arouse intrinsic ventricular activity with sympathomimetic drugs 51 times. Epinephrine was effective in 18 of 24 trials in doses ranging from 5 to 44 μg. per minute (average 20 μg. per minute). In 5 instances the ineffective doses ranged from 10 to 19 μg. per minute; larger amounts were not given because of excessive elevation of the blood pressure. In the sixth instance, in a patient dying of cerebral damage, 64 μg. per minute were given without cardiac effect.

Isoproterenol was effective in 19 of 20 trials in doses ranging from 5 to 43 μg. per minute (average 12 μg. per minute). In the 1 ineffective trial no more than 13 μg. per minute were given because of a fall in blood pressure. Although the average effective dose of isoproterenol was somewhat less than that of epinephrine, the difference was not statistically significant.

Levarterenol was given 7 times because of hypotension during absent intrinsic ventricular activity. The amounts given (3 to 32 μg. per minute) had a striking vasopressor effect but did not arouse ventricular pacemakers; on 1 occasion transient atrioventricular conduction was recorded (see fig. 9).

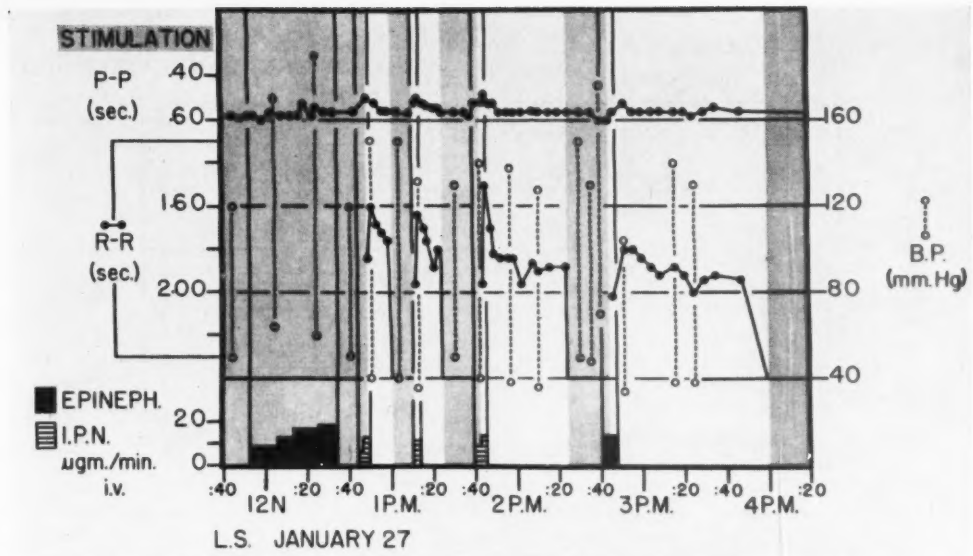
Observations of the effects of these drugs in accelerating and maintaining ventricular pacemakers were made after ventricular activity had been aroused and also on 12 occasions when an idioventricular pacemaker was already established. In these trials both epinephrine and isoproterenol were potent and effective. Quantitative documentation of these actions will not be presented because they are already well known[1, 2] and our data, obtained during primarily therapeutic administration, are limited and incomplete.

Figure 1 shows electrocardiograms and figure 2 presents quantitative data illustrating the arousal and acceleration of an intrinsic ventricular pacemaker by epinephrine. At 10:55 a.m., after 10 hours during which ventricular beats occurred only with external stimulation (fig. 1*A*), epinephrine was given intravenously at a rate of 8 μg. per minute. Within 5 minutes, after the total infusion of 40 μg. of epinephrine, the P-P interval shortened and an idioventricular pacemaker appeared with an R-R interval of 1.87 seconds (32 beats per minute) (fig. 1*B*); thereupon the electric pacemaker was stopped. The idioventricular pacemaker accelerated rapidly to a cycle length of 1.32 seconds (45 beats per minute) (fig. 1*C*) and the epinephrine was stopped at 11:05 a.m. The idioventricular pacemaker began to slow and its rate declined steadily to an R-R interval of 2.82 seconds (21 beats per minute) at 12:27 p.m. when syncope occurred. At this moment electric stimulation was resumed (fig. 1*D*) with an immediate rise of blood pressure and return of consciousness. Two minutes later a test interruption of stimulation (fig. 1*E*) showed that intrinsic ventricular activity was again absent.

Figure 3 shows in another patient the repeated arousal, acceleration, and maintenance of an idioventricular pacemaker by epinephrine. The drug was given after 90 hours during which ventricular beats occurred solely in response to external electric stimuli. Dependence of the ventricular rhythm upon the drug was demonstrated repeatedly by the disappearance or abrupt slowing of the ventricular pacemaker whenever epinephrine was omitted. Finally, 21 hours after the beginning of epinephrine administration, the ventricular rhythm persisted at a satisfactory rate when the drug was stopped.

The effect of levarterenol was then tested upon this stable ventricular pacemaker. As expected, the blood pressure rose and there was a concomitant reflex slowing of the sinoatrial rate; the independent ventricular pacemaker, however, accelerated sharply. When the R-R interval had shortened to 1.38 seconds (43 beats per minute), a new ventricular pace-

*Supplied through the courtesy of Winthrop Laboratories.



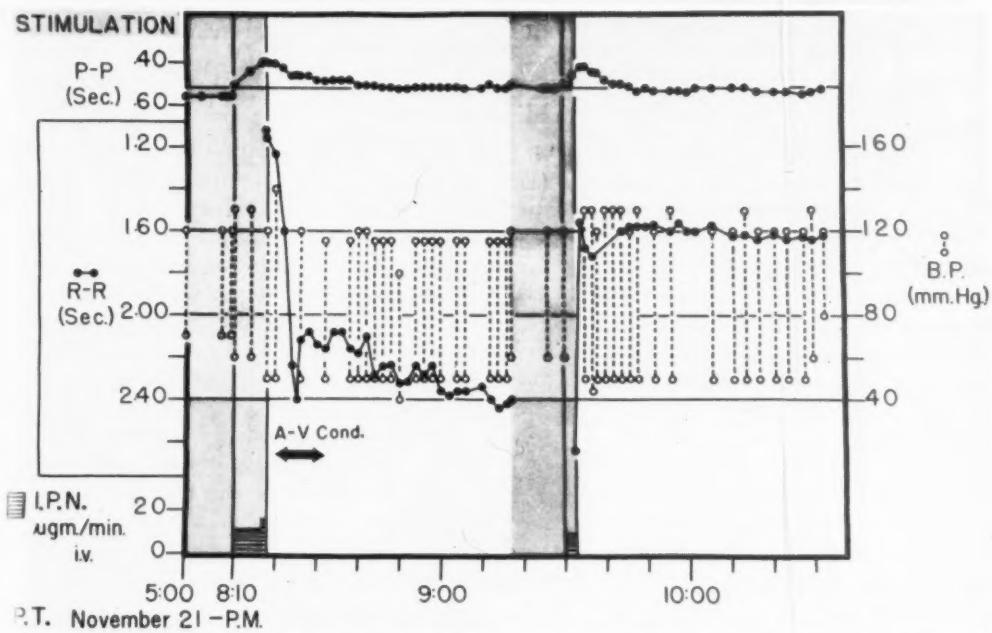


FIG. 4 *Top.* Comparison of epinephrine and isoproterenol (I.P.N.) in arousing ventricular activity. The initial trial of epinephrine, which was started at 11:51 a.m., was stopped at 12:35 p.m. because of a marked pressor response without arousal of intrinsic ventricular activity. Isoproterenol at 12:42, 1:10, and 1:40 p.m., and epinephrine at 2:40 p.m. promptly aroused idioventricular pacemakers. Each time omission of the drug was followed by disappearance of spontaneous ventricular activity, which necessitated resumption of external electric stimulation.

FIG. 5 *Bottom.* Variability of ventricular rhythmicity after 2 isoproterenol (I.P.N.)-induced arousals. Isoproterenol administration started at 8:10 p.m. aroused an initially fast ventricular pacemaker, cycle length 1.14 seconds (54 beats per minute). The rate slowed promptly with cycle lengths varying between 2.10 and 2.40 seconds (29 and 25 beats per minute), and occasional conducted beats occurred until 8:32 p.m. External electric stimulation was resumed at 9:16 p.m. because of the slowing ventricular rate, whereupon spontaneous activity ceased. At 9:32 p.m. a smaller dose of isoproterenol aroused the pacemaker again. This time, however, it stabilized promptly at a cycle length of 1.60 seconds (38 beats per minute).

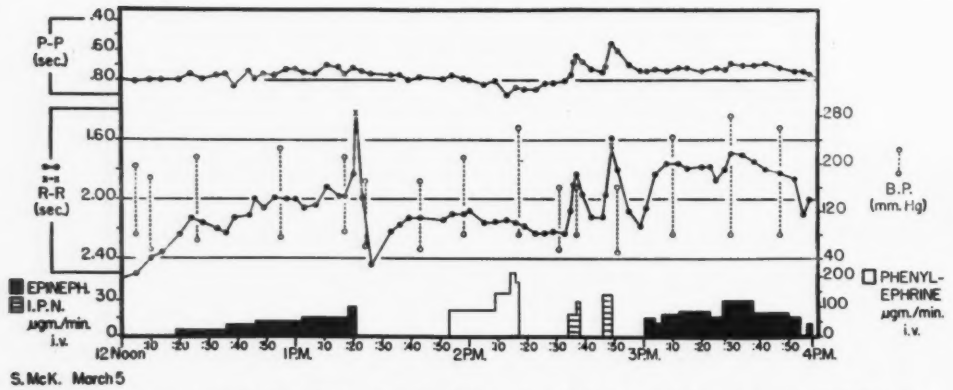


FIG. 6. Comparison of the effects of epinephrine, phenylephrine, and isoproterenol (I.P.N.) on ventricular rhythmicity and blood pressure during complete heart block. Epinephrine, administered in varying doses at 12:18 and 3:00 p.m., accelerated the ventricular rate markedly and produced a transient change in ventricular focus (X). Isoproterenol, administered at 2:33 and 2:46 p.m., had similar marked effects on the ventricle; in addition it produced striking sinoatrial acceleration. Phenylephrine, administered at 1:52 p.m., had no effect on the ventricular rate even though the dose had a marked vasopressor effect.

maker appeared, which continued to accelerate to a cycle length of 1.23 seconds (49 beats per minute). Then levarterenol was stopped and this potentially toxic sequence was reversed promptly.

The efficacy of epinephrine and isoproterenol in arousing intrinsic ventricular activity was compared by administering them in varying order and in close sequence to 9 patients. No superiority of one drug over the other was demonstrated.

In figure 4 the effects of epinephrine and isoproterenol in arousing a ventricular pacemaker were compared after 12 hours of continuous external electric stimulation. Five observations were carried out within a 3-hour period from an apparently similar baseline of absent intrinsic ventricular activity. An initial attempt to arouse a ventricular pacemaker with epinephrine failed but 3 subsequent trials of isoproterenol and a final trial of epinephrine aroused transient ventricular activity. Comparison of the effects of isoproterenol with the initial epinephrine trial suggests a marked difference between the 2 drugs. However, the final epinephrine observation indicates a similar effectiveness of these agents.

The variability of drug effect on the heart is strikingly illustrated again in figure 5. In 2 closely spaced trials isoproterenol readily aroused a ventricular pacemaker; other cardiac effects of the 2 doses, however, differed strikingly, even though they were given to the same patient so closely together and from the same baseline of absent intrinsic ventricular activity. In the first trial the basic ventricular pacemaker slowed progressively and was interrupted by occasional conducted beats and frequent beats from other slow ventricular foci; in the second trial the ventricular pacemaker stabilized promptly and persisted at a much faster rate than before with only a few multifocal beats. This change in response emphasizes the caution necessary in quantitating and in comparing the cardiac effects of drugs.

On 1 occasion phenylephrine was compared with epinephrine and isoproterenol (fig. 6). In a dose that produced a marked rise in blood pressure, phenylephrine did not accelerate the ventricle. In contrast, epinephrine and isoproterenol produced marked ventricular acceleration and change in focus with variable blood pressure responses.

Cardiac Toxicity

Phenomena suggesting potential cardiac toxicity were observed with each sympathom-

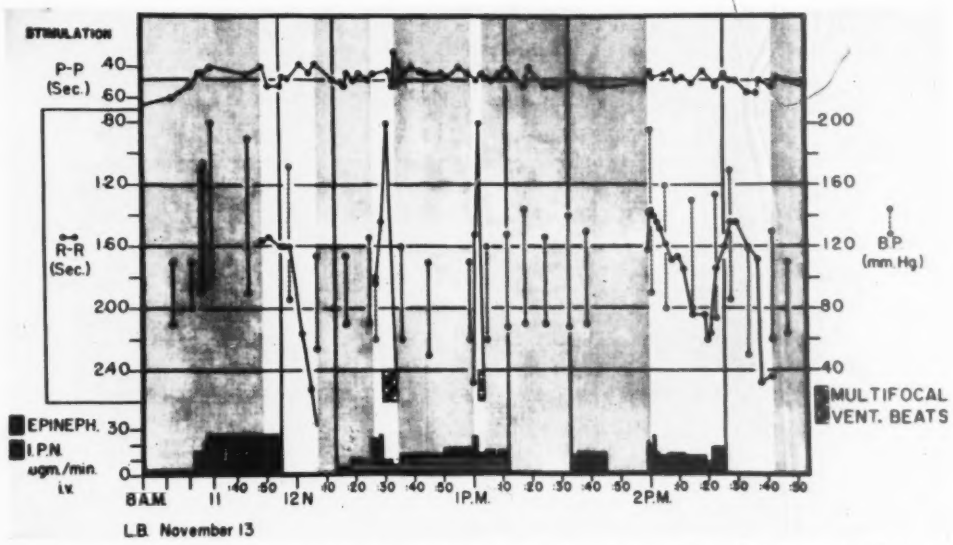


FIG. 7. Comparison of therapeutic effect (arousal of ventricular pacemaker) versus toxic effects (excessive acceleration and multifocal ventricular activity) of epinephrine and isoproterenol (I.P.N.). Isoproterenol at 12:27 and 1:00 p.m. aroused ventricular activity that was transient and was marked by excessive acceleration to a cycle length of 0.84 second (71 beats per minute) and multifocal ventricular beats. Epinephrine, on the other hand, at 11:48 a.m. and 2:00 p.m., aroused slower, and more persistent ventricular rhythms without multifocal beats.

metic drug tested. These effects, which were considered to be possible forerunners of ventricular tachycardia or fibrillation, were acceleration of idioventricular pacemakers above 50 beats per minute (R-R = 1.2 seconds) and the appearance of premature beats after an interval of less than 1.2 seconds. The limit of acceleration was placed at this rate of 50 beats per minute, which we consider safe and sufficient for almost all therapeutic purposes and which is well below the level of acceleration found by Schwartz[8] to precede ventricular fibrillation. Multifocal ventricular activity at a rate slower than 50 beats per minute (R-R more than 1.2 seconds), whether it occurred as single beats or as shifts among dominant pacemakers, is often seen spontaneously in complete heart block[9] and therefore was not considered ominous. Of particular concern were rapid ventricular rhythms from new or multiple foci and premature beats that were very frequent or that came from multiple foci. Premature beats that fall on the preceding T waves have also been described as being particularly ominous,[9, 10] but we observed none.

Potential cardiac toxicity was observed with epinephrine and isoproterenol in 10 patients: excessive ventricular acceleration (over 50 beats per minute) 6 times and premature beats 5 times with isoproterenol; excessive acceleration twice and premature beats 4 times with epinephrine. Whenever these signs of potential toxicity were observed, administration of drugs was slowed or stopped, whereupon the untoward manifestations disappeared promptly. Serious clinical toxicity of ventricular tachycardia of more than a few beats' duration or ventricular fibrillation never occurred in the course of this drug therapy. One paroxysm of atrial tachycardia due to epinephrine was observed. It lasted only a few seconds, stopping after omission of the drug, and was of no clinical significance.

Usually, excessive acceleration or premature beats occurred when the drug dose was continued or increased after a therapeutic effect had been obtained. Sometimes, however,

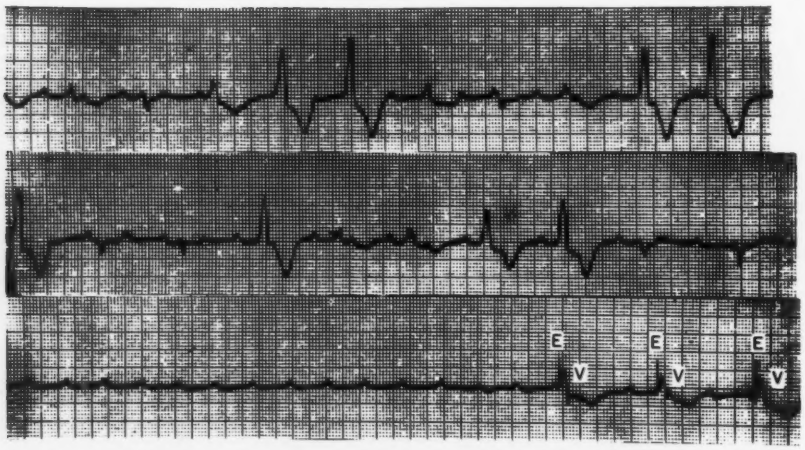


FIG. 8. Continuous electrocardiogram (lead aV_F) during second isoproterenol trial (fig. 7, 1:01 p.m.), showing arousal of multifocal ventricular tachycardia followed by ventricular standstill requiring external electric stimulation (E and V).

the toxic effect could not be dissociated from the therapeutic one. As shown in figure 7, for example, isoproterenol twice aroused an intrinsic ventricular pacemaker but multifocal ventricular activity and tachycardia occurred at the same time. On the second trial the dose of isoproterenol that produced the tachycardia was inadequate to maintain ventricular activity and the ensuing standstill required electric stimulation (fig. 8). In contrast, epinephrine in 2 trials shortly before and after the isoproterenol, aroused and maintained an intrinsic ventricular pacemaker without the production of multifocal beats.

Increase in Atrioventricular Conduction

Another cardiac effect of sympathomimetic amines is to increase atrioventricular conduction. This may occur as an isolated effect (fig. 9) or together with other cardiac responses to the drugs (figs. 5 and 10). This phenomenon was observed 17 times in 6 patients: 4 times with epinephrine, 12 times with isoproterenol, and once with levarterenol. All 6 patients showed occasional spontaneous atrioventricular conduction of some degree; nevertheless it was clearly established that the drugs also increased conduction. The doses of the drugs that produced this effect were in the same range as the doses that aroused ventricular pacemakers: 5 to 15 μg. per minute of epinephrine and 4 to 22 μg. per minute of isoproterenol. Varying degrees of conduction were observed, from occasional beats to normal 1 : 1 atrioventricular conduction. Atrioventricular conduction was transient, lasting from a few seconds (fig. 9) to 45 minutes (fig. 10); this phenomenon, therefore, was of little clinical value although of considerable theoretical interest.

Figure 9 shows transient, partial atrioventricular conduction due to administration of levarterenol during a prolonged period of external electric stimulation. The only other cardiovascular effect of the drug was a slight elevation of the blood pressure. Idioventricular activity was not aroused; when conduction failed there was ventricular standstill with syncope requiring immediate resumption of external stimulation.

Figure 10 shows the appearance of atrioventricular conduction together with the acceleration and maintenance of an idioventricular pacemaker with the administration of isoproterenol. Other cardiovascular effects were sinoatrial acceleration and fall in blood pressure. With the first 2 trials, 2 : 1 atrioventricular conduction occurred. During th

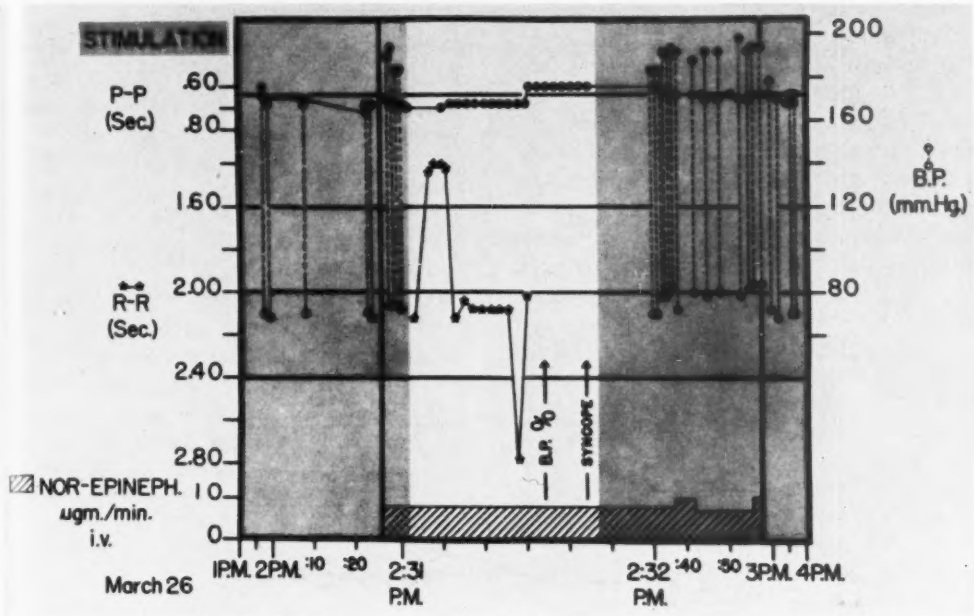


FIG. 9. Restoration of partial atrioventricular conduction for 45 seconds by levarterenol (*norepineph.*). With a sinoatrial cycle of 0.70 second, the ventricular cycles were 1.40 seconds (2:1), 2.10 seconds (3:1), and 2.80 seconds (4:1).

third drug trial, when the rate of administration was fastest, a step-by-step sequence was observed from complete block to 1 : 1 atrioventricular response. The repeated appearance of atrioventricular conduction with each trial of isoproterenol established the conclusion that the drug caused this change.

Effects of Sodium Lactate on Ventricular Rhythmicity

In view of the reported therapeutic value of intravenous molar sodium lactate in Stokes-Adams disease,[7] we also tested its action in arousing or accelerating an idioventricular pacemaker in 5 patients.

In 1 patient who had been without intrinsic ventricular activity for 26 hours, 200 ml. of molar sodium lactate were administered in 6 minutes without effect. After half an hour, trial of sympathomimetic amines was started; epinephrine and isoproterenol, in sequence, both aroused ventricular activity.

In 3 patients there was slight acceleration of an established idioventricular pacemaker: after 100 ml. in 11 minutes, the R-R interval shortened from 3.56 to 2.76 seconds (17 to 22 beats per minute); after 150 ml. in 20 minutes, it changed from 1.40 to 1.28 seconds (43 to 47 beats per minute); and after 90 ml. given in divided doses in 1 hour, it shortened from 1.89 to 1.69 seconds (32 to 36 beats per minute). In 2 of these patients variable atrioventricular conduction was seen spontaneously or following administration of epinephrine; contrary to observations by others,[7] atrioventricular conduction did not increase after sodium lactate in these patients. The fifth patient (fig. 11), who received 70 ml. in 12 minutes, showed a slight but definite slowing of the ventricular rate; sodium lactate then was stopped because of the appearance of frequent premature ventricular beats and bigeminy. In striking contrast was the marked acceleration observed in this patient after epinephrine and isoproterenol. A very few premature ventricular beats were also seen

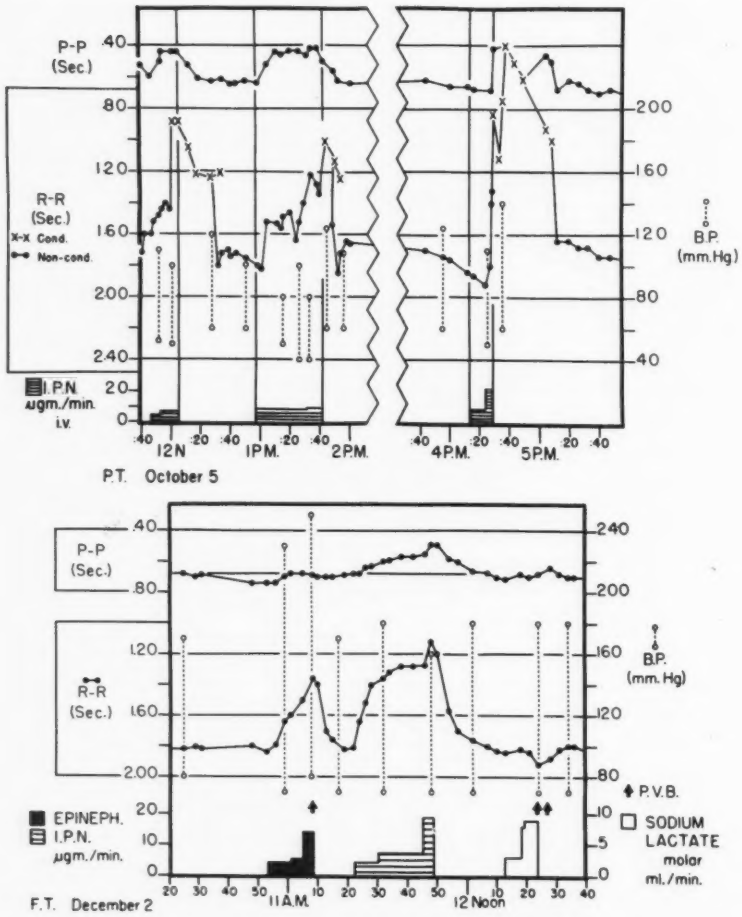


FIG. 10 *Top.* Repeated acceleration of idioventricular pacemaker and restoration of atrioventricular conduction (2:1 and 1:1) by isoproterenol (I.P.N.). Isoproterenol administered at 11:45 a.m., 12:55, and 4:15 p.m. accelerated the idioventricular rate (●) and also produced atrioventricular conduction (X).

FIG. 11 *Bottom.* Comparison of epinephrine, isoproterenol (I.P.N.), and sodium lactate in accelerating an idioventricular pacemaker and in exciting premature ventricular beats. Epinephrine, administered at 10:53 a.m., accelerated the ventricular rate, excited occasional premature ventricular beats, and elevated the blood pressure. Isoproterenol, administered at 11:22 a.m., accelerated the ventricular rate even more without producing premature beats or raising the blood pressure. In contrast, sodium lactate, administered at 12:12 p.m., slowed the ventricular rate slightly and produced frequent premature ventricular beats and bigeminy.

at the height of the epinephrine acceleration, but none occurred with the isoproterenol.

Our large experience with sympathomimetic amines indicating their safety and efficacy, the relatively slight ventricular acceleration with sodium lactate, and the reported toxicity of this drug[7, 11] have deterrred us from testing this agent further. Therefore we have not systematically compared molar sodium lactate with sympathomimetic agents in arousing intrinsic beats in patients with persistent ventricular standstill.

Discussion

These observations show clearly the effectiveness and safety of epinephrine and isoproterenol administered intravenously in dilute solutions for the arousal, acceleration, and maintenance of intrinsic ventricular activity. For arousal, the effective intravenous dose was often only a small fraction of the usual subcutaneous dose: for example, only 40 μg. (8 μg. per minute for 5 minutes) of epinephrine (fig. 2) compared to 200 to 500 μg. The rapid appearance and disappearance of the effects of the drug contribute to safety by permitting moment-to-moment control. By the same token constant supervision is required; such close attention is feasible for emergencies but is impractical for long-term administration. For prolonged acceleration and maintenance, epinephrine, isoproterenol, and ephedrine may be given by other routes.

These rapid and clear-cut responses permit reliable measurements of the effects of these drugs and some comparisons of their actions. The striking differences in effects of the same agent in closely spaced trials in the same patient (figs. 4 and 5) indicate a change in cardiac responsiveness, even though the baseline for each trial was apparently the same in that there was no spontaneous ventricular activity. This change makes the comparison of different agents particularly difficult. Such difficulties would be multiplied by attempts at comparisons at widely spaced intervals or in different patients. The factors that produce such changes in cardiac responsiveness are unknown. Analogous, inexplicable sudden changes in ventricular rhythmicity account for the striking unpredictability that is so prominent a clinical feature of Stokes-Adams attacks and that complicates the evaluation of drug therapy.

If cardiac responsiveness remains unchanged, as demonstrated by uniform effects of the same drug at the beginning and end of a test period, fairly valid comparisons can be made, however, from a baseline of either absent ventricular activity or of a stable idioventricular rate. For example, in figure 7, the production of ectopic activity by isoproterenol sandwiched between fairly uniform responses to epinephrine without ectopic activity permits the conclusion that isoproterenol was more toxic in this patient at this time. The somewhat different observation in another patient, shown in figure 11, suggests the opposite conclusion that epinephrine was more toxic than isoproterenol. Variations of this kind from patient to patient emphasize the danger of generalizations about comparative toxicity on the basis of limited data.

In choosing between epinephrine and isoproterenol for patients with Stokes-Adams disease, one must consider the effectiveness of each drug in arousing, accelerating, and maintaining a ventricular pacemaker versus the risk of exciting ectopic ventricular activity. It has recently been stated[12, 13] that isoproterenol is superior to epinephrine because its effective dose is smaller and because it does not lead to ventricular tachycardia or fibrillation. The latter conclusion is based in one instance[12] on a comparison in 1 patient of the effects of a single dose of each drug administered a day apart; the other instance[13] described the clinical course of 2 patients, one of whom received epinephrine and subsequently isoproterenol, and the other of whom was treated only with isoproterenol. These observations exemplify the difficulties of comparison we have just enumerated and do not justify the conclusion reached by the authors.

From our studies a figure cannot be given for the minimal effective dose and for the therapeutic/toxic ratio of each drug. The dose of each drug necessary to arouse a ventricular pacemaker varied widely from patient to patient and at different times in the same patient. Data on toxicity were necessarily limited to fortuitous observations in these clinical studies. In this regard we are carrying out detailed quantitative studies of sympathomimetic drugs in dogs with surgically produced, permanent complete heart block.[14]

Nevertheless, our many observations of these 2 drugs permit the general conclusion that there is no striking difference in their cardiac effects. Both agents were very effective in arousing, accelerating, and maintain-

ing a ventricular pacemaker in doses that were not significantly different. In any case, differences in doses are not an important basis of comparison; considerations of safety are of much greater clinical significance. Both drugs produced minor toxicity, in the form of excessive acceleration and premature ventricular beats, which disappeared promptly when drug administration was stopped. These untoward manifestations were infrequent and occurred about equally with both drugs.

Clear differences between the 2 drugs lie in their effects on the blood pressure and on the sinoatrial rate. Epinephrine usually had a marked pressor effect, whereas isoproterenol had no effect or lowered the blood pressure. Isoproterenol usually accelerated the sinoatrial rate markedly, whereas the effect of epinephrine was comparatively slight (figs. 6 and 11). In patients with atrioventricular conduction this action of isoproterenol may result in a rapid ventricular rate with untoward clinical manifestations. In figure 10, for example, at 4:38 p.m. the ventricular rate rose to 150 beats per minute (R-R = 0.40 second) as a result of sinoatrial acceleration and 1 : 1 atrioventricular conduction, both due to isoproterenol. Considerations of these actions often determined our initial choice. If the first drug was ineffective or toxic, we frequently tried the other agent, often with success.

Levarterenol, another widely used sympathomimetic amine, had cardiovascular effects quantitatively different from those of epinephrine and isoproterenol. Its major action was a striking vasopressor one. Although we did not observe it to restore intrinsic ventricular activity, it did accelerate a ventricular pacemaker that was already present and it did excite multifocal ventricular beats. These effects on cardiac rhythmicity are of clinical importance as toxic manifestations when the drug is used as a vasopressor agent in the treatment of shock.[15] In 1 observation (fig. 6) phenylephrine in a vasopressor dose had no effect on the idioventricular pacemaker. Further observations of this type may uncover the vasopressor agent that carries minimal risk of exciting ventricular tachycardia or fibrillation.

Our experience with molar sodium lactate is too limited for adequate evaluation of this drug in Stokes-Adams disease. It accelerated the ventricle only slightly in comparison with epinephrine and isoproterenol, yet it produced ectopic ventricular activity. These observations suggest a relatively low efficacy in arousal and acceleration of ventricular rhythm and a relatively small therapeutic/toxic ratio.

In addition to stimulating ventricular rhythmicity, epinephrine, isoproterenol, and levarterenol increased atrioventricular conduction. This effect on conduction was transient and therefore was not clinically significant. This observation has been reported by others in man[16, 17] and is related to the experimental demonstration that epinephrine shortens the refractory period and increases the speed of atrioventricular conduction.[18] All the patients in whom we saw this effect of drugs, at other times had spontaneous variations in atrioventricular conduction of the type that has been termed paroxysmal or intermittent heart block.[19, 20] These changes in conduction in patients with complete heart block are of great theoretical interest: they indicate a functional component as well as an organic basis for heart block and suggest the possibility that a clinically useful drug may be found to increase and maintain atrioventricular conduction.

Intravenous Administration of Sympathomimetic Drugs in the Treatment of Stokes-Adams Disease

The technics of external electric stimulation and defibrillation permit the emergency resuscitation of patients from Stokes-Adams attacks. There are 2 other problems, however, in the management of this disease: persistent absence of intrinsic ventricular activity and frequent recurrence of attacks.[5] The intravenous administration of epinephrine or isoproterenol is often indicated to arouse, accelerate, or maintain intrinsic ventricular pacemakers. When the idioventricular pacemaker slows markedly or stops frequently, the drugs may stabilize the ventricular rate at an ade-

quate level and stop the seizures, making electric stimulation unnecessary.

After the resuscitation of a patient with Stokes-Adams disease from ventricular standstill with the external electric pacemaker, stimulation should be stopped promptly to see whether intrinsic ventricular activity has returned. If a satisfactory and stable ventricular pacemaker (at least 25 beats per minute) is not present, external electric stimulation must be continued. Since prolonged stimulation in the conscious patient is usually painful, it is often desirable to arouse intrinsic ventricular activity without delay. Therefore, if intrinsic ventricular activity remains absent for 1 hour or more, epinephrine or isoproterenol should be administered intravenously according to the technic and with the precautions we have described. The ventricular pacemaker aroused by drugs may be unstable and may require prolonged continuous regulation of the drug infusion. In this situation, it is often preferable to stop drug administration, to return to the dependable electric pacemaker for as long as desired, and then to try drugs again.

Considerations of the different effects of these 2 drugs on the blood pressure and on the sinoatrial rate often determine the initial choice. In patients with high blood pressure isoproterenol is preferable, since it has no vasopressor action; when the pressure is normal or low, epinephrine is the drug of choice. In patients who have recently had atrioventricular conduction epinephrine should be used, since it is a much less potent accelerator of the sinoatrial pacemaker than is isoproterenol and there is, accordingly, less risk of a rapid ventricular rate should atrioventricular conduction return. Familiarity with a drug and its ready availability may also influence the initial selection.

Intravenous administration of the drug should be started at a rate of 4 μg. per minute (15 drops or 1 ml. of a solution containing 4 mg. of the drug in 1 L. of 5 per cent dextrose in water), and its effects should be observed electrocardiographically during frequent short interruptions of electric stimulation. Every few minutes the rate of infusion should be increased by increments of 4 to 8 μg. per minute until a ventricular pacemaker is aroused or until cardiac or systemic toxicity is produced in the form of frequent or multifocal premature ventricular beats, ventricular acceleration faster than 50 beats per minute, excessive rise or fall of the blood pressure, or excessive stimulation of the central nervous system. If the first drug fails to arouse a satisfactory ventricular pacemaker or if it produces toxicity, its administration should be stopped and the other drug should be tried subsequently.

When a ventricular pacemaker is aroused, the rate of drug administration should be adjusted until the idioventricular rate is between 35 and 45 beats per minute. When the ventricular rate has stabilized in this range, the rate of drug administration should be gradually slowed and then stopped if the ventricular rate is maintained.

Frequent Stokes-Adams attacks due to recurrent slowing or disappearance of the ventricular pacemaker constitute a second indication for the intravenous administration of epinephrine or isoproterenol. In this situation also, either drug may stabilize the ventricular rate between 35 and 45 beats per minute and prevent further attacks.

At this point, when a satisfactory ventricular rate has been achieved, other therapy, such as oral ephedrine or sublingual isoproterenol, may be instituted for the long-term management of Stokes-Adams disease. We have observed that seizures are unlikely to recur after 1 month has passed without an attack. During this period it is important to observe the patient closely and to have an external electric pacemaker in emergency readiness.

Summary

The effects of intravenously administered epinephrine, isoproterenol, levarterenol, phenylephrine, and sodium lactate on ventricular rhythmicity and atrioventricular conduction have been studied in 83 drug trials in 21 patients with Stokes-Adams disease.

Epinephrine and isoproterenol in dilute

solutions were equally effective in arousing ventricular pacemakers in patients without intrinsic ventricular activity while they were being kept alive by prolonged external electric cardiac stimulation. Both drugs were also effective in accelerating and maintaining ventricular activity. Minor cardiac toxicity (excessive ventricular acceleration above 50 beats per minute or premature ventricular beats), occurring equally with both drugs, was an indication to slow or stop drug administration; major cardiac toxicity (persistent ventricular tachycardia or fibrillation) did not occur. In addition, both epinephrine and isoproterenol occasionally produced transient increase in atrioventricular conduction.

Levarterenol, in addition to its marked vasopressor action, also affected ventricular rhythmicity and atrioventricular conduction whereas phenylephrine had only a vasopressor effect. Differences of this nature may prove important in the selection of a sympathomimetic amine for a particular cardiovascular effect.

Limited observations of sodium lactate showed it to be less effective than epinephrine and isoproterenol in arousing and accelerating ventricular pacemakers.

Summario in Interlingua

Le effectos de administrationes intravenose de epinephrina, de isoproterenol, de levarterenol, de phenylephrina, e de lactato de natrium super le rhythmicitate ventricular e super le conduction atrioventricular esseva studiate in 83 essayos in 21 patientes con morbo de Stokes-Adam.

Epinephrina e isoproterenol in diluite solutiones non differeva in lor efficacia in stimular pacemakers ventricular in patientes sin intrinsec activitate ventricular qui esseva tenite in vita per medio de prolongate externe electrostimulation del corde. Le duo drogas habeva etiam le effecto de accelerar e mantener le activitate ventricular. Minor grados de toxicitate cardiac (excessos de acceleration ventricular supra 50 pulsos per minuta o prematur pulsos ventricular) occurreva con le un e con le altere del duo drogas e esseva prendite como indication pro relentar o arrestar le administration. Formas major de toxicitate cardiac (persistente tachycardia o fibrillation ventricular) non occurreva. In plus, tanto epinephrina como etiam isoproterenol produceva in certe casos augmentos transiente de conduction atrioventricular.

Levarterenol, a parte su marcate action vasopressori, etiam afficeva le rhythmicitate ventricular e le conduction atrioventricular, durante que phenylephrina habeva solmente un effecto vasopressori. Differentias de iste genere va frequentemente provar se importante in le selection de un amina sympathomimetic pro evocar un specific effecto cardiovascular.

Minus extense observationes de lactato de natrium monstrava que illo es inferior a epinephrina e isoproterenol como stimulator e accelerator de pacemakers ventricular.

Acknowledgment

We wish to acknowledge the technical assistance of Mrs. Lee Goodman and Mrs. Beverly Fordyce.

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The searching into the works of Nature, while it delights and inlarges the mind, and strikes us with the strongest assurance of the wisdom and power of the divine Architect, in framing for us so beautiful and well regulated a world, it does at the same time convince us of his constant benevolence and goodness towards us.—*Statistical Essays.* Reverend Stephen Hales. From the Dedication to His Royal Highness, George, Prince of Wales. Volume I, The Second Edition, London, 1731.

Infradiaphragmatic Total Anomalous Pulmonary Venous Connection

By Arnold L. Johnson, M.D., F. W. Wiglesworth, M.D., J. S. Dunbar, M.D., Sarjit Siddoo, M.D., and Maria Grajo, M.D.

A study of 4 cases of uncomplicated total anomalous pulmonary venous drainage, in which the connection with the systemic circuit is in the region of the porta hepatis, revealed similar clinical and radiologic findings, so that in the fourth case the diagnosis was suspected and confirmed by angiocardiographic study. Mainly due to the obstruction of pulmonary venous outflow, this form of total anomalous pulmonary venous drainage forms a distinct entity and the physiologic disturbance is quite different from those anomalies of the venous return in which the connection with the systemic circulation is above the diaphragm.

TOTAL anomalous pulmonary venous return in which the connection with the systemic circuit occurs below the diaphragm forms a separate entity that is in striking contrast with the total anomalous pulmonary venous connections in the thorax. The infradiaphragmatic form is quite distinct, mainly because of partial obstruction to pulmonary venous return in the region of the porta hepatis. A study of 4 uncomplicated cases in which the common pulmonary vein passed through the diaphragm to join the systemic circulation in the region of the porta hepatis revealed clinical and radiologic features that permit a reasonable suspicion of the true diagnosis, which may then be established by angiocardiographic means. Seventeen cases (table 1) of this variety of anomalous pulmonary venous connection have been found in the literature but no diagnostic criteria have hitherto been established. It should be noted that this type of anomalous pulmonary venous connection may occur in association with a variety of cardiac malformations. These complicated cases are not included in this study, since they do not then represent a clinical entity.

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Presented in part at The Fifth Inter-American Congress of Cardiology, Havana, Cuba, November 11 to 17, 1956.

Clinical Findings

In view of the similar anatomic arrangement it is not surprising that the clinical findings in our 4 patients were similar. All were male and age at death was 12 days, 22 days, 22 days, and 23 days (table 2). All were dyspneic and cyanotic. In 1 case, a grade III systolic murmur was heard, maximal in the fourth left intercostal space at the left edge of the sternal border, but no murmur was heard in the remaining 3 cases. The intensity of the pulmonic second sound in the case of D.S. was considered to be normal, while no comment was made regarding this sound in the other 3 cases. The liver was enlarged in 3 cases.

Electrocardiograms obtained in 2 of the cases are compatible with the right ventricular hypertrophy demonstrated at necropsy (fig. 1).

The x-ray examination was of the greatest importance. The appearance of the lungs is an unusual one at this age. There is a reticular appearance due to minute, scattered, irregular areas of increased density. This was seen well in the films of B.F., D.S., and G.W., but in the case of B.O. evidence of pneumonia was present, and this pattern was not evident. In each instance on the films the heart was not

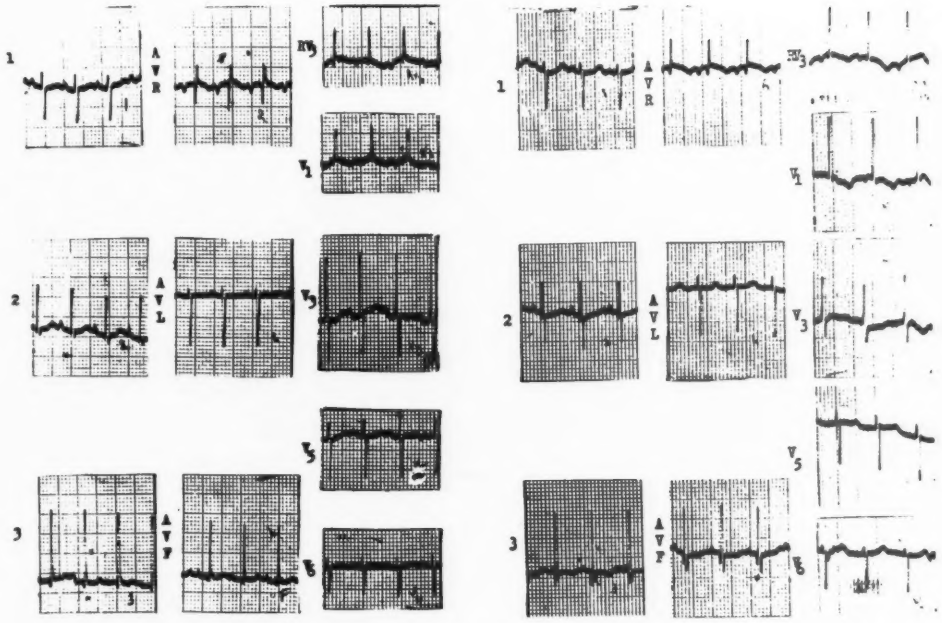

FIG. 1. Electrocardiograms of D.S. at age 10 days (*left*) and B.F. at age 12 days (*right*).

considered to be enlarged or abnormal in contour. Fluoroscopic examination was performed in the case of G.W. and the heart size was seen to be normal and no particular chamber enlargement was evident. In D.S. the right ventricle was considered to be enlarged by this method of examination.

It can hardly be maintained that the radiologic appearance of the lungs is diagnostic for this condition. It may be confused with multifocal pneumonia in the newborn and with conditions included under the heading of the newborn respiratory distress syndromes: hyaline membrane disease, atelectasis of the newborn, amniotic fluid aspiration, and pulmonary hemorrhage. These all produce a diffuse increase in density in the lungs with multiple reticular or punctate shadows. A review of our cases of these conditions has suggested that as a rule the shadows are finer and more uniform than in the cases of infradiaphragmatic pulmonary venous return.

Inasmuch as the correct diagnosis was suspected on the basis of the clinical and x-ray findings in D.S. and supported by angiocardiographic studies, a summary of this case history is presented.

D.S.: Approximately 11 hours after birth this infant became suddenly cyanotic and had considerable respiratory distress and remained so, despite some relief with oxygen therapy, until death on the twenty-second day. There was a

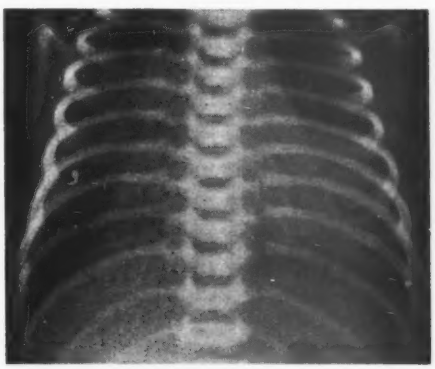

FIG. 2. Posteroanterior projection of chest in case D.S. at 9 days of age, showing reticulated appearance of lungs.

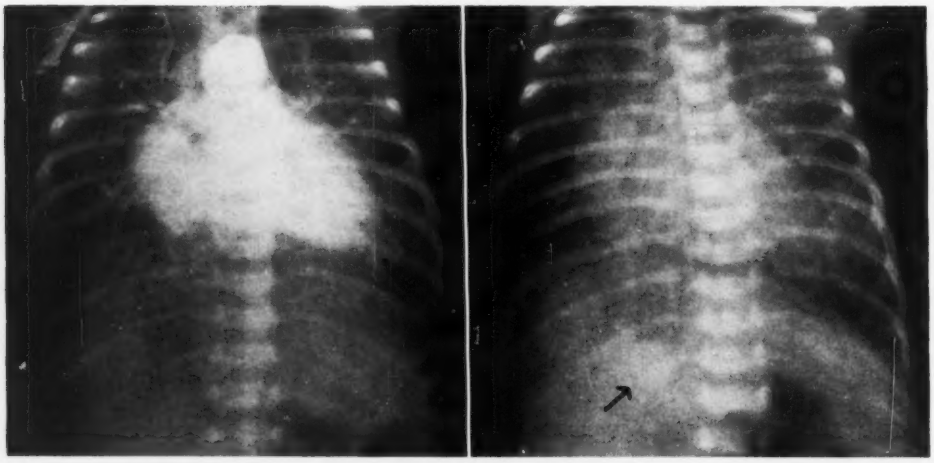

FIG. 3. *Left.* Simultaneous opacification of aorta and large pulmonary artery, 2 seconds after injection. *Right.* Note shadow of contrast media in region of porta hepatis 9 seconds after injection.

grade III, moderately harsh systolic murmur, maximal at the fourth intercostal space to the left of the left sternal border. The pulmonic second and the mitral first sounds were normal. The liver remained 3 fingerbreadths below the right costal margin in the midclavicular line. There did not appear to be a definite improvement with digitalization.

The electrocardiogram (D.S. at age 10 days) is shown in figure 1.

On x-ray (fig. 2) there did not appear to be any generalized cardiac enlargement, but on fluoroscopic examination the appearance was suggestive of some right ventricular enlargement. No right or left atrial enlargement was detected. The left aortic arch and the pulmonary artery appeared normal. The hilar vascular markings were average in density and no pulsations were seen in them. The lungs appeared to be overinflated and there were numerous fine, irregular shadows, resulting in

TABLE 1.—*Cases of Uncomplicated Infradiaphragmatic Total Anomalous Pulmonary Venous Return*

No.	Date	Author	Sex	Age at death	Site of entry of common pulmonary vein
1	1916	Ghon[1]	M	15 days	Portal vein
2	1933	Munck[2]	M	3 mos.	Portal vein
3	1948	Mykschowsky[3]	M	18 days	Portal vein
4	1950	Edwards and DuShane[4]	M	9 days	Ductus venosus
5	1952	Butler[5]	M	2 days	Portal vein
6	1952	Parsons et al[6]	F	4 wks.	Ductus venosus
7	1953	Bor[7]	F	10 wks.	Portal vein
8	1954	Keith et al.[8]	M	21 days	Portal vein
9	1956	Gott et al.[9]	?	?	Portal vein
10	1957	Darling et al.[10]	M	6 wks.	Portal vein
11	—		M	3 wks.	Portal vein
12	—		M	5 wks.	Portal vein
13	1957	Rosenfeld et al.[11]	F	4 wks.	Portal vein
14	1957	This series	M	23 days	Portal vein
15			M	12 days	Ductus venosus
16			M	22 days	Portal vein
17			M	22 days	Region of porta hepatis

a reticulated appearance of the lung fields. It was this appearance, together with the cyanosis, dyspnea, hepatomegaly, and unresponsiveness to digitalization, that suggested the possibility of an infradiaphragmatic anomalous venous connection.

In the angiocardiographic examination (fig. 3 *Left*) the contrast medium showed early and simultaneous opacification of the aorta and main pulmonary artery, indicating a right-to-left shunt. The pulmonary artery was larger than normal. The contrast medium was widely distributed throughout the pulmonary vascular tree but it was not until 9 seconds after the injection (fig. 3 *Right*) that a circular shadow appeared below the diaphragm in the region of the porta hepatis. It was evident that there was a significant delay in pulmonary venous return and that at least some portion of the contrast medium had gained this infradiaphragmatic position after the contrast medium had been cleared from the aorta. It could most reasonably have arrived there by way of an anomalous pulmonary venous connection.

On postmortem examination the abnormal findings were confined to the heart and lungs. There was moderate dilatation and hypertrophy of the right atrium and right ventricle (fig. 4) and an aneurysmal bulging of the valvula foraminis ovalis. No pulmonary veins entered the left atrium, which was normal in size, as was also the left ventricle. Two pulmonary veins from each lung joined together to form a common trunk (fig. 5), which lay anterior to the esophagus and passed inferiorly with it and posterior to the heart and through the diaphragm to drain into the left portal vein at the porta hepatis.

The lungs were moderately congested, somewhat rubbery to palpation and only moderately aerated. On microscopic examination there was marked passive congestion of the alveolar walls (fig. 6) with tortuosity and bulging of the capillaries into the alveolar sacs and heart failure cells were present. Hemosiderin-laden histiocytes were present in the alveolar walls as well as in the interstitial tissues. The liver showed no evidence of passive congestion and there was no splenomegaly.

Pathologic Anatomy

The pathologic features were similar in all 4 cases. There was an increase in the size of the right atrium and the right ventricle in each case, consisting of some dilatation and hypertrophy of each of these chambers. The size of the left atrium and ventricle was probably normal but relatively small in comparison with the right chambers. The valvula foraminis ovalis showed an aneurysmal bulging in D.S., while the other 3 cases showed incompetence of the valvula foraminis ovalis. The pulmonary artery was minimally dilated in 3 cases while in the fourth, B.F., it was not. The aorta was normal in all. The ductus arteriosus was probe-patent in all cases.

There was no patent connection between the pulmonary veins and the left atrium. In 2 cases, however, a solid fibrous cord joined the left atrium to the pulmonary veins near the junction to form the common pulmonary vein (fig. 7). The common pulmonary vein was formed in each instance by the junction of the pulmonary veins from each lung and lay

TABLE 2.—*Infradiaphragmatic Total Anomalous Pulmonary Venous Return, Clinical Features*

Case	Sex	Age (days)	Cyanosis	Dyspnea	Murmurs	Sounds	Liver	X-ray		E.C.G.
								Heart size (P.A. view)	Lungs	
D.S.	M	23	11 hrs. after birth	+	Grade III S.M. max. fourth LIS	P_2 & M_1 normal	3 fb.	Normal	Reticulated appearance	RVH
B.F.	M	12	At birth	+	None	Not commented upon	At umbilicus	Normal	Reticulated appearance	RVH
B.O.	M	22	At birth	+	None	Not commented upon	2 fb.	Normal	Bilateral pneumonia	Not recorded
G.W.	M	22	2 days after birth	+	None	Not commented upon	1 fb.	Normal	Reticulated appearance	Not recorded

FIG. 4 *Top.* Cross section of heart of D.S. on the left with a normal control on the right. The right ventricle is uppermost in both specimens.

FIG. 5 *Bottom.* Dissection of pulmonary veins and their communications in case of D.S. Lungs above. Liver below. *1*, Left pulmonary vein; *2*, right pulmonary vein; *3*, common pulmonary vein; *4*, left portal vein; *5*, right portal vein; *6*, portal vein; *7*, umbilical vein; *8*, ductus venosus; *9*, inferior vena cava.

anteriorly to the esophagus, passing inferiorly through the diaphragm at the esophageal hiatus. It entered the ductus venosus in the case of B.F., the portal vein in B.O., the left portal vein in D.S., and its site of entry was not definitely determined in G.W. The diameter of the common pulmonary vein in the fixed state was 0.6 cm. just after the union and 0.3 cm. distally near the liver.

The microscopic examination of the lungs showed evidence of subacute to chronic pas-

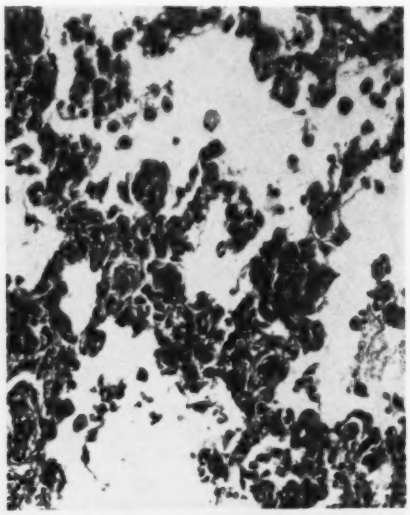

FIG. 6 *Top.* Lung showing marked passive congestion with heart failure cells in alveolar sacs. Note thick-walled arteriole to the left of center suggesting presence of hypertension. Contrast with figure 8. Hemalum, phloxin, saffron, ×190.

FIG. 7 *Bottom.* Photograph to show the fibromuscular cord connecting the left atrium with the common pulmonary vein (case B.O.). The heart has been turned up opposite the apices of lungs, which are viewed from the posterior aspect. A probe lies in the common pulmonary vein formed by 4 pulmonary veins.

sive congestion. The alveolar walls were thickened as a result of marked congestion of the capillaries, as well as edema. Definite fibrosis could not be demonstrated. There was a moderate degree of hemosiderosis with iron deposited both in the alveolar walls and in the interstitial tissues. The pulmonary arterioles were thick walled with tiny lumens as compared with controls but no measurements were made. In none of the cases was passive congestion of the liver demonstrated.

The fibrous cord joining the left atrium to the common pulmonary vein was serially cross-sectioned and found to consist of areolar tissue and atrial muscle bundles, running longitudinally. No patent or obliterated lumen was found. This presumably is the stem of the common pulmonary vein and suggests that agenesis of the common vein is not necessary for the development of abnormal pulmonary vein drainage.

Circulatory Disturbances

It is difficult to know if the fetal circulation is embarrassed by this malformation. The fact that the pulmonary venous return is small in amount suggests that it might be handled without difficulty. On the other hand, the degree of the right ventricular hypertrophy and the marked microscopic lung changes noted by 12 days of age might indicate that the flow from the lungs suffered significant obstruction prior to birth.

In postnatal life the circulation is seriously impaired by 3 major disturbances. The first is the obstruction provided to drainage of the pulmonary venous return because of the limited cross-sectional area of the common pulmonary vein, ductus venosus, or portal vein. If the flow is into the ductus venosus, all the pulmonary blood flow might pass directly to the inferior vena cava. If, however, the common pulmonary vein enters the portal vein, the pulmonary flow, as previously noted by Edwards and DuShane,[4] might all pass through the liver or might be distributed in part by the way of the hepatic sinusoids and in part by the ductus venosus. It is thus apparent that obstruction provided to pulmonary venous return is similar to that in mitral stenosis, and the microscopic lung sections have shown changes similar to those noted in this valvular obstruction. The second major circulatory disturbance is that all the venous return of the body, both systemic and pulmonary, is handled by the right side of the heart. The third is the occurrence of the right-to-left shunt at the atrial level.

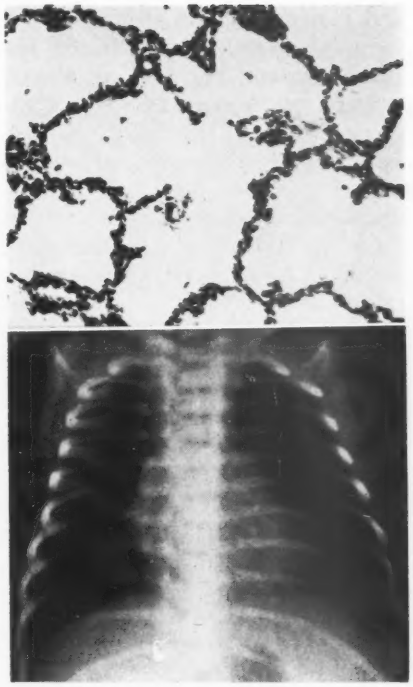

FIG. 8 *Top.* Lung in case of complicated infradiaphragmatic venous return with pulmonary atresia. Note complete normality of lung as compared with figure 6. Hemalum, phloxin, saffron, ×190.

FIG. 9 *Bottom.* Posteroanterior projection of the chest. B.B.E., age 5 days. Note reduction in the pulmonary vascular markings.

In commenting upon the abnormal circulation in this malformation, Edwards and Du Shane[4] noted that the pulmonary congestion is a reflection of the obstruction to pulmonary venous outflow. Because of this stenosis in the pulmonary circuit and the right-to-left shunt, they likened the disturbed circulation to that in a tetralogy of Fallot. It is hard to concur in

this view when the site of the obstruction makes such a crucial difference in the pulmonary hemodynamics, the pulmonic stenosis of a tetralogy preventing adequate pulmonary inflow, and that of this lesion, like mitral stenosis, preventing adequate pulmonary outflow.

An instructive case in point is provided by our fifth case (B.B.E.) of infradiaphragmatic anomalous pulmonary venous return to the portal vein that was complicated by an atresia of the pulmonary valve with hypoplasia of the pulmonary arteries, and a transposed aorta arising from the right ventricle. It is significant that in the presence of this reduced pulmonary blood flow, the microscopic examination of the lungs (fig. 8) reveals a normal vascular pattern and the absence of heart failure cells and of hemosiderosis. Reduction in the density of the hilar vascular markings, compatible with a reduced pulmonary blood flow, had been apparent in the chest x-ray in this case (fig. 9).

Embryology

The lung bud is differentiated from the ventral surface of the foregut and with its development there occurs an outgrowth from the splanchnic plexus from which the pulmonary veins are formed. The splanchnic plexus has connections with the anterior and posterior cardinal venous systems and with the umbilicovitelline system, so that initially the pulmonary plexus also has these extensive connections above and below the diaphragmatic level. With the growth of the liver, the umbilicovitelline system is gradually differentiated to form the hepatic veins, the liver sinusoids, and the portal vein. Certain hepatic sinusoids are differentiated to form the ductus venosus and provide a direct route for placental blood from the left umbilical vein to the sinus venosus. The common pulmonary vein as shown by Neill[13] develops as an outgrowth from the medial superior wall of the left atrium and joins the venous plexus of the developing lung bud. If this union fails to occur, this plexus will drain into a common channel associated with the esophagus and enter the portal venous system by way of the portal vein or ductus venosus.

The presence in 2 of our cases of a fibrous cord extending from the left atrium to the origin of the common pulmonary vein may indicate that there has been a secondary obliteration of the common pulmonary vein between the left atrium and the pulmonary plexus, a possibility suggested by Edwards.[12] The other possibility that he noted appears to obtain in the other cases in which no residual structure was found, suggesting that there was agenesis of the common pulmonary vein.

Discussion

The malformation under discussion is not a common one. Over a 23-year period, 1933 to 1955, The Montreal Children's Hospital autopsy series included 300 cardiac anomalies. Fifteen had total anomalous pulmonary venous return, of which 10 drained into the systemic circuit above the diaphragm and 5 drained infradiaphragmatically. Of the latter, 4 are the cases reported here and the fifth was complicated by the presence of pulmonary atresia, already referred to in connection with the discussion of the changes in the lungs.

The predominant male sex distribution has already been commented upon by Darling.[10] In table 1 the sex is known in 16 of the 17 cases and 13 are male. Neglecting the unspecified case the sex ratio in this sample differs from equality at the 2 per cent level. If the unspecified case is a female, the difference is significant only at the 5 per cent level. If it turns out to be a male, the difference is significant almost at the 1 per cent level.*

In the performance of autopsies on infants, it is important always to lift up the apex of the heart to note the position of the insertion of the pulmonary veins, prior to the removal or cutting of these structures. Otherwise the exact details of an anomalous pulmonary venous drainage will be lost forever.

Diagnosis may have a more than academic

*We are indebted to Dr. F. C. Fraser, Director, Department of Genetics, The Montreal Children's Hospital, for this statistical analysis.

interest because the mobility, diameter, and length of the common pulmonary vein would allow for an anastomosis to the left atrium, which in our 4 cases, appeared to be of adequate size to accept the pulmonary venous return.

Summary

Four uncomplicated cases of total anomalous pulmonary venous return, in which the connection with the systemic circuit is by a common vein passing infradiaphragmatically to enter in the region of the porta hepatis, are presented. Reports of 13 previous similar cases were found. This infradiaphragmatic form of anomalous pulmonary venous return is quite distinct from the supradiaphragmatic form because of the partial obstruction to pulmonary venous return, the pathologic findings in the lungs being similar to those of mitral stenosis.

Clinical suspicion of the presence of this lesion is based upon the occurrence of dyspnea and cyanosis in the first few days of life in an infant with an average heart size by x-ray but with a peculiar pulmonary vascular x-ray pattern. Angiocardiography in the 1 case so studied confirmed the diagnosis.

Summario in Interlingua

Es presentate 4 non-complicate casos de anormal total retorno pulmono-venose in que le connexion con le circulation systemic es effectuate per un vena commun a passage infradiaphragmatic e entrata in le region del porta hepatic. Esseva trovate reportos de 13 simile casos in le litteratura. Iste forma infradiaphragmatic de anormalitate del retorno pulmono-venose es clarmente differentiate ab le forma supradiaphragmatic, viste le obstruction partial del retorno pulmono-venose e le facto que le constatationes pathologic in le pulmones es simile a illos trovate in stenosis mitral.

Le suspicion clinic del presentia de iste lesion es justificate si dyspnea e cyanosis occurre durante le prime dies del vita de un infante con normal dimensiones roentgenologic del corde in association con un roentgenogramma distinctive del vasculatura pulmonal. Angiocardiographia confirmava le diagnose in le caso unic in que illo esseva usate.

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Long-Term Treatment of Angina Pectoris with Dicumarol

By ZETH GABRIELSEN, M.D†., AND JON R. MYHRE, M.D.

By the use of "report cards" the daily amount of anginal pain and the weekly consumption of nitroglycerin tablets were registered in a small series of patients during alternating courses of Dicumarol and a placebo, covering in all more than 2 years. The total number of Dicumarol periods was 24, half of them lasting more than 6 months. The effect of Dicumarol was evaluated.

DURING the last few years reports have appeared of the favorable therapeutic effect of anticoagulants on pain in cases of angina pectoris. Heparin at first had its advocates, but later the possibility of reducing the severity and frequency of the anginal attacks through the use of this drug has been seriously disputed.[1, 2] At present the use of Dicumarol and allied drugs is considered more promising. Remarkably good results from the protracted use of these drugs have been reported,[3-7] and some authors have even found marked improvement after a few days of treatment.[4, 8] Most workers base their conclusions on personal interviews or written questionnaires issued to the patients. These and some other methods for the evaluation of drug effect on cardiac pain have been severely criticized by Greiner and associates,[9] who emphasize the many fallacies, especially the influence of suggestion, and the necessity of adequate control material. In the present study a small group of patients with angina pectoris receiving alternately Dicumarol and a placebo has been followed for more than 2 years by the use of a technic described by Greiner and co-workers.[9] The results do not support the claims of a beneficial effect of Dicumarol on the anginal pain.

MATERIAL AND METHODS

Our material comprises 10 normotensive individuals, 9 men and 1 woman, suffering from arteriosclerotic heart disease and angina pectoris (table 1).

Four of the subjects had previously suffered from acute myocardial infarction with resulting typical and lasting electrocardiographic changes. In the other cases the resting electrocardiograms were normal, and the diagnosis was based on clinical criteria. A positive electrocardiogram after work or hypoxia presented additional diagnostic evidence, in all cases except 1 (no. X). Hypercholesterolemia (over 400 mg. per cent) was found in 3 cases, especially severe and accompanied by marked tendon xanthomata in no. VI, our youngest patient. None of the subjects suffered from congestive heart failure at the beginning of the study, but moderate failure gradually developed in case no. X. The heart size was normal in all cases except in this subject.

BRING THIS CARD TO CLINIC NEXT VISIT
How much pain in the heart did you have each day?

Day of the Week	Same Heart Pain as Usual	Less Heart Pain Than Usual—Good Day	More Heart Pain Than Usual—Bad Day	No Heart Pain at All
Monday				
Tuesday				
Wednesday				
Thursday				
Friday				
Saturday				
Sunday				

Before going to bed, each day, write a mark (X) in the space that describes your heart pain for the entire day.

FIG. 1. The "daily report card."

For registration of the anginal pain we used the "daily report cards" of Greiner and co-workers[9] (fig. 1). The card covers 1 week and allows a grading of the separate days. To obtain from the cards a numerical expression of the patient's condition during each whole week it was decided to use the following scale:

A day of no cardiac pain	0
A day of less than usual pain	1
A day of pain as usual	2
A day of more than usual pain	3

By adding the values for the separate days of

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†Deceased October 27, 1957.

TABLE 1.—*Pertinent Data on Ten Cases of Angina Pectoris*

Case no.	I	II	III	IV	V	VI	VII	VIII	IV	X
Age (years) and sex	60 M	45 M	54 M	61 M	59 M	42 M	46 M	59 M	50 F	58 M
Hypercholesterolemia (>400 mg. per cent)	+	−	−	−	+	+	−	−	−	−
Duration of angina pectoris (years)	1	1	6	8	1	5	2	1	2	10
Previous myocardial infarct (years before study)	1	−	−	1	−	1	?	−	−	−

the week, a sum representing the whole week was obtained. The figures for each week of the total period of observation were used as a basis for the evaluation of the information gained from the report cards.

The effect of Dicumarol on the blood coagulability was tested weekly by the prothrombin-proconvertin method of Owren,[10, 11] the aim being to keep the values between 15 and 30 per cent. No episodes of bleeding or other complications of anticoagulant therapy were encountered. The prothrombin-proconvertin level was below 35 per cent during 85 per cent of the Dicumarol treatment periods.

At the initiation of the study subject no. VI had already been treated with Dicumarol for 2 weeks. The others all went through a "control period" of approximately 2 months' duration before any tablets, except the usual nitroglycerin tablets, were administered. Thereafter Dicumarol tablets and placebo tablets were administered in alternating courses for more than 2 years in each case. Blood samples were collected regularly also during the placebo periods.

The placebo tablets were exact replicas of the drug tablets in size, appearance, and consistency, and, as far as we could judge, also in taste. They were made from starch and lactic acid and "flavored" with a little quinine.

A fresh supply of tablets was issued when the patients visited the hospital for blood coagulability control. The "daily report cards" were collected at the same time. No attempts were made to register the condition of the patients during these visits, all duties being performed by a nurse with only the most necessary information concerning the difference between the placebo tablets and the drug tablets. Conditions closely approximating the "double blind" requirements were thus obtained.

The duration and number of the different periods are apparent from figure 2. The whole study covers 8,498 patient days or 1,214 patient weeks. The "control periods" account for 7 per cent of the time, 55 per cent represents the Dicumarol periods and 38 per cent the placebo periods. The total number of Dicumarol periods is 24, of which 3 were of less than 4 months' duration, 9 lasted between 4 and 6 months, 5 between 6 and 8 months, and 7 lasted between 8 and 11½ months.

Six subjects managed to keep count of their consumption of nitroglycerin tablets, recording on their report cards the amount of tablets used per week. In this way additional evidence for the evaluation of their condition was obtained. It might be tempting to consider the information concerning the nitroglycerin consumption as more "objective" and accordingly more valuable than the information concerning the pain. As pointed out by other workers,[9] however, many factors other than pain influence the use of nitroglycerin tablets.

RESULTS

Our results are graphically recorded in figure 2. As might be expected, the curves for anginal pain and for nitroglycerin consumption show a rather varying course, although we have chosen not to plot the values for each single week, but have used the biweekly averages. One subject, no. III, died suddenly after 22 weeks of continuous Dicumarol therapy and before any placebo treatment had been administered. The clinical picture was that of an acute myocardial infarction.

The pain report curves remained at approximately the same levels during the whole period of observation. No systematic tendency could be seen toward lower curve levels at the end of the Dicumarol periods, indicating improvement, or higher levels, indicating deterioration, at the end of the placebo periods. A marked pain reduction seemed to have taken place in cases nos. VI and VIII toward the end of the first year. In case no. VI the

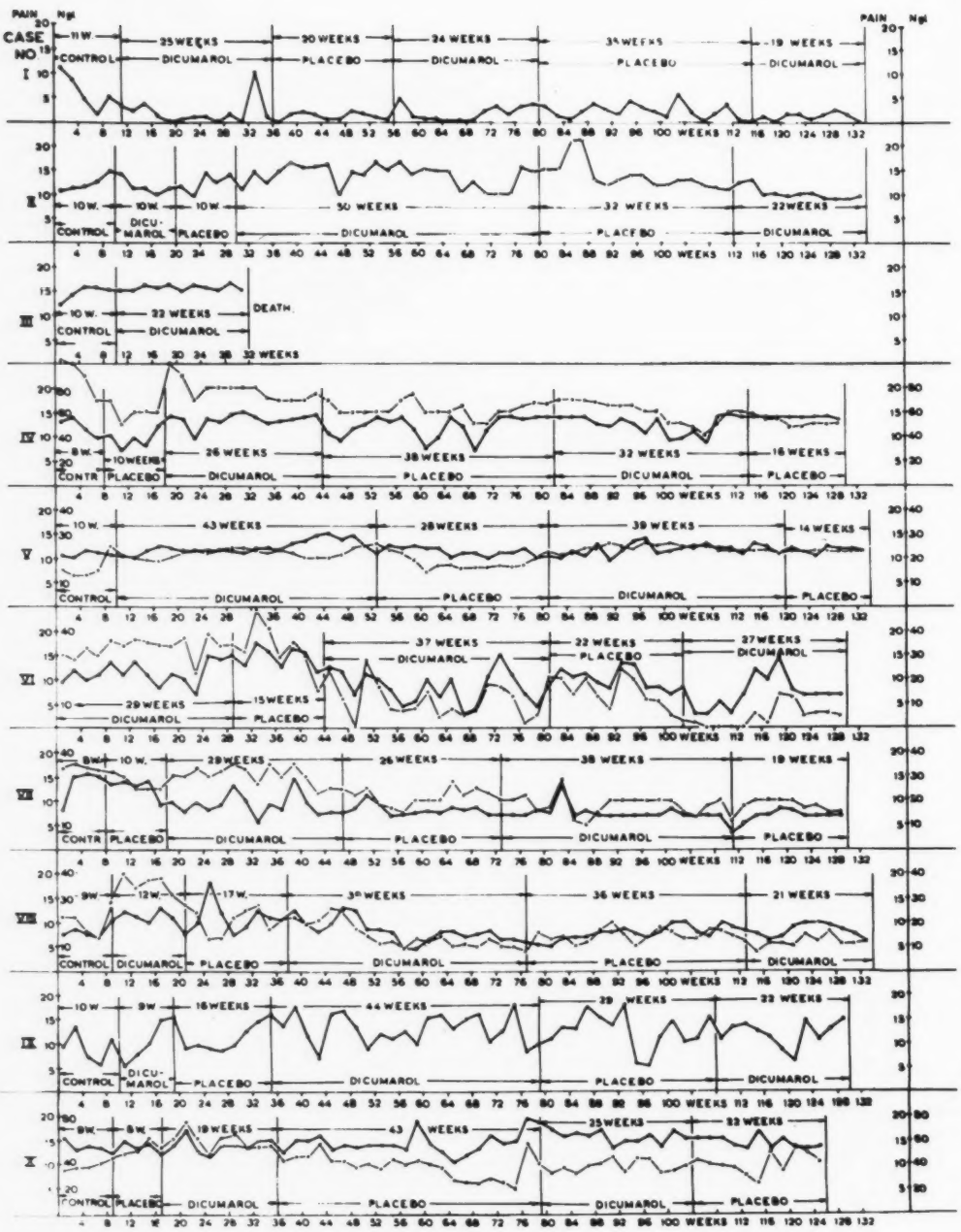

FIG. 2. Graphic presentation of the values for pain as calculated from the daily report cards (*unbroken line*) and of the values for the consumption of nitroglycerin tablets (*broken line*). *Ordinate*, scale for pain values on left and for nitroglycerin consumption on right.

TABLE 2.—*Average Weekly Values for Pain and Nitroglycerin Consumption During the First and Last Four Weeks of the Dicumarol Periods and the Placebo Periods*

Case no.		Dicumarol periods		Placebo periods	
		First 4 weeks	Last 4 weeks	First 4 weeks	Last 4 weeks
I	Pain	2.0	3.2	1.4	0.9
	Ngl.				
II	Pain	12.7	11.6	12.6	12.3
	Ngl.				
III	Pain	15.0	15.8		
	Ngl.				
IV	Pain	13.9	14.3	11.9	13.9
	Ngl.	83	66	61	59
V	Pain	10.4	12.1	11.8	11.1
	Ngl.	21	24	24	21
VI	Pain	9.0	9.3	12.8	10.0
	Ngl.	16	15	28	14
VII	Pain	7.8	6.8	7.1	7.2
	Ngl.	25	21	20	19
VIII	Pain	10.0	7.9	8.4	9.9
	Ngl.	22	18	18	17
IX	Pain	11.4	13.0	11.1	13.8
	Ngl.				
X	Pain	15.9	15.6	14.6	16.0
	Ngl.	49	46	45	50

improvement started rather suddenly after a 15-week period of placebo tablets. In case no. VIII the curve started falling after approximately 10 weeks of Dicumarol treatment, declined for another 10 weeks, and remained more or less stationary during the ensuing periods.

The 6 nitroglycerin consumption curves for long intervals ran remarkably parallel to the pain report curves, following closely even minor variations. The decline of the pain report curves of cases nos. VI and VIII was equally marked in the corresponding nitroglycerine consumption curves. A rather marked fall in nitroglycerin consumption also took place during the first Dicumarol periods

TABLE 3.—*Statistical Analysis of Average Values for Pain and Nitroglycerin Consumption*

	Degrees of freedom	Mean square	Variance ratio (F)
Pain values			
Dicumarol/placebo	1	1.0	0.1
Error	130	7.1	
Nitroglycerine consumption.			
Dicumarol/placebo	1	240.0	3.0
Error	109	80.7	

Conditions during the last 4 weeks of all the Dicumarol periods (case III excepted) and all the placebo periods are compared by variance analysis. No difference is found on the 5 per cent significance level.

of cases nos. IV and VII. However, in the preceding placebo period of case no. IV the consumption was lower than during any time of the Dicumarol period in question, an isolated high peak during the first part of the Dicumarol period being a more conspicuous feature than the ensuing decline. In case no. VII the fall in nitroglycerin consumption started after approximately 22 weeks of Dicumarol treatment. Both in this case and in case no. VIII it might look as if the nitroglycerin consumption curves indicated a therapeutic effect of the drug. Since the nitroglycerin consumption curve of case no. VI showed a decline as pronounced as the pain report curve during the first placebo period, and a steady and marked fall occurred during placebo treatment from the forty-fourth to the seventy-sixth week in case no. X, it is evident that an explanation along these lines is scarcely tenable.

Table 2 gives the weekly averages for pain and nitroglycerin consumption during the first 4 weeks and the last 4 weeks of all Dicumarol and placebo periods for each individual.

These composite figures from the beginning and the end of the periods of each type of treatment might disclose any systematic tendency better than do the curves. The pain values are, however, much the same in all

columns, while a tendency toward reduction in nitroglycerin consumption during both Dicumarol periods and placebo periods is evident. A comparison between the nitroglycerin consumption during the last 4 weeks of each type of treatment discloses in 5 out of 6 cases, however, a higher average nitroglycerin consumption during the end of the Dicumarol periods than during the end of the placebo periods.

The results have also been evaluated by statistical methods. A comparison of the pain report values and the nitroglycerin consumption values for the last 4 weeks of each type of treatment discloses no significant difference between the therapeutic effect of the Dicumarol tablets and the placebo tablets (table 3).

Discussion

Keeping in mind the numerous errors that have been made in all fields of therapy while trying to evaluate new types of treatment, and considering the special difficulties encountered when the therapeutic efficacy on a purely subjective phenomenom like pain is to be judged, we think that the greatest caution should be exerted in formulating any conclusions. We feel justified in stating only that in this material, with the doses and courses of Dicumarol here administered, and with the methods of registration here employed, no specific beneficial effect could be traced from the use of Dicumarol in the treatment of the anginal pain.

Summary

An attempt was made to register by use of "report cards" the daily amount of pain and the weekly consumption of nitroglycerin tablets in 10 cases of angina pectoris during treatment by alternating courses of Dicumarol tablets and placebo tablets. Four subjects had previously suffered from myocardial infaretion. All had had their symptoms for at least 1 year, and in 4 cases for more than 3 years. One died shortly after the initiation of the study, and only 6 managed to keep count of their nitroglycerin consumption. The total number of Dicumarol periods was 24, half of them lasting more than 6 months, during a total period of observation lasting for more than 2 years.

The results do not indicate that Dicumarol treatment has a greater effect than a placebo treatment on the cardiac pain in cases of angina pectoris of more than 1 year's duration.

Summario in Interlingua

Esseva tentate registrar per medio de "cartas de reporto" le grados diurne de dolor e le consumption septimanal de tablettas de nitroglycerina in 10 casos de angina de pectore durante cursos alternante de therapia per tablettas de Dicumarol e per tablettas de medication fictitie. Quatro del subjectos habeva previemente suffrite de infarcimento myocardial. Omnes habeva habite lor symptomas durante al minus 1 anno, 4 durante plus que 3 annos. Un del subjectos moriva brevemente post le initiation del studio, e solmente 6 succedeva a mantener le reportos de lor consumption de nitroglycerina. Le numero total del periodos de administration de Dicumarol esseva 24. Un medietate de illos durava plus que 6 menses. Le periodo total del observationes esseva plus que 2 annos.

Le resultatos non indica que Dicumarol exerceva un plus forte effecto que le medication fictitie super le dolores cardiac in casos de angina de pectore de un duration de plus que 1 anno.

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Each case has its lesson—a lesson that may be, but is not always, learnt, for clinical wisdom is not the equivalent of experience. A man who may have seen 500 cases of pneumonia may not have the understanding of the disease which comes with an intelligent study of a score of cases, so different are knowledge and wisdom, which as the poet truly says, 'far from being one, have oft-times no connexion.'—*Aequanimitas and Other Addresses.* Blakiston & Co., Philadelphia, and T. K. Lewis, London, 1904.

Bronchoscopic Method for Measuring Left Atrial Pressure

An Aid to Diagnosis in Mitral Disease

By A. J. Gunning, M.B., F.R.C.S., and R. J. Linden, M.B., Ch.B.

The possibility is examined that measurements from the records of left atrial pressure obtained by direct puncture of the left atrium through the bronchoscope might help in the diagnosis of mitral disease. The left atrial pressure records of 156 patients have been analyzed and the results are presented.

IT WAS suggested that the record of left atrial pressure, obtained through the bronchoscope, might help to differentiate between mitral stenosis and mitral regurgitation and also to distinguish those patients in whom the mitral lesion is not the major cause of the symptoms.[1]

The validity of these suggestions has been tested in a series of 156 patients.

Method

The apparatus used was the same as that previously described by Allison and Linden.[1, 2] The manometer system was damped only by the puncturing needle and the degree of damping was 60 to 70 per cent of the critical value. It must be emphasized that in a system of this type no other damping is required. If, to eliminate artifacts, further damping is applied by electric or mechanical means, the amplitude of the recorded pressure pulse will be reduced, and inaccuracies of an unknown degree will occur.

The Patient. At rapid heart rates the records of the left atrial pressure contours are less accurate: (1) because the ratio of the frequency of the impressed force to the natural frequency of the manometer system is large and this causes distortion; and (2) because, in some patients with mitral disease and atrial fibrillation, regurgitation may occur when the heart rate is slow and may not be present when the rate is faster.[1]

In an investigation by this method the fact that the patient does not have a general anesthetic and is aware of the surroundings tends to increase the heart rate. To avoid tachycardia, therefore, it is advisable to give a vagal-stimulating drug such as morphia and withhold any vagal-paralyzing drug such as atropine. If the patient is apprehensive, additional sedation with a barbiturate may be necessary. The most important factors are adequate explanation and reassurance of the patient.[3]

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Records. Pressure records were obtained with the center of the manometer membrane level with the upper edge of the manubrium sterni, and this point was taken as the zero reference point in all figures. In all tracings an electrocardiogram and a phonocardiogram were recorded to facilitate the recognition of the individual waves of the pressure pulse contours. The method of measuring the records has been described previously,[1] but is briefly reviewed. The cardiac cycles to be examined were chosen from those that occurred during the expiratory phase. Pressures were then measured at 2 points in the atrial cycle: at the "Z" point,[4] which is a point on the atrial pressure curve just before the beginning of the "c" wave, and at the top of the "v" wave. These 2 points of the atrial pressure curve correspond to the beginning and end of ventricular systole. A calculation was then made of the "mitral value" as described and discussed previously:[1] the difference between the pressures at the "V" and the "Z" points (P_V-P_Z) is expressed as a percentage of the pressure at the top of the "v" wave (P_V). It is important to select the correct points on the curve at which to measure the pressures; these are illustrated in figure 1, which shows records from patients with sinus rhythm and with atrial fibrillation.

Selection of Material. The records of patients accepted for this study were taken in order according to the numbers in the departmental files; but this is not truly an unselected series, as mere attendance at a thoracic surgical clinic infers some degree of selection.

The cases were divided into groups, first according to the clinical diagnosis and, second, according to the findings at operation. The diagnoses of mitral stenosis, mitral regurgitation, and combined lesions were made from the now well-described symptomatology, physical signs, and radiology of these variations of rheumatic heart disease.[5-7] The size of the mitral orifice was determined by the surgeon's finger; a method has been described by Goodwin et al.,[6] who expressed the size of the orifice in terms of the distance between the commissures. They arranged their cases in

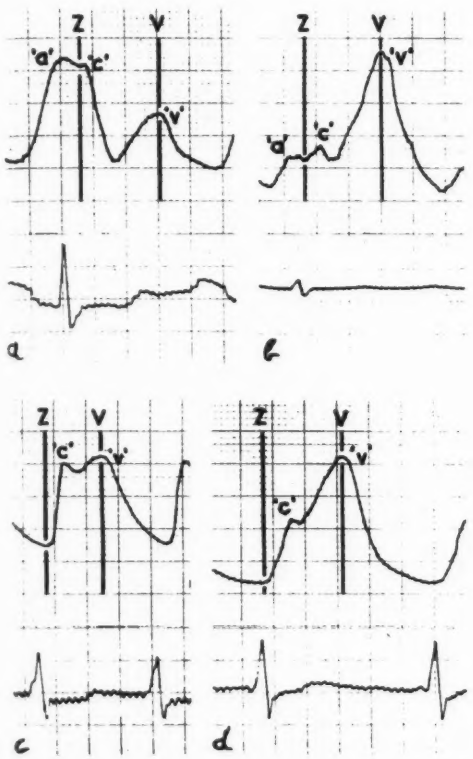

FIG. 1. Diagram to show the position of the 'Z' and 'V' points. Single cardiac cycles from the records of each of 4 patients: *a*, sinus rhythm and mitral stenosis; *b*, sinus rhythm and mitral regurgitation; *c*, atrial fibrillation and mitral stenosis; *d*, atrial fibrillation and mitral regurgitation. Upper curve in each record, left atrial pressure pulse; lower curve electrocardiogram. In each cycle the 'a,' 'c,' 'v' waves of the venous pulse are indicated; the position of intersection of each vertical line with the atrial curve indicates the point at which the pressure was measured.

the following groups: critical mitral stenosis less than 1.0 cm., severe 1.0 to 1.5 cm., moderate 1.5 to 2.0., and minimal when the commissures were more than 2.0 cm. apart. However the surgeon's assessment may not be absolutely accurate because he is calculating this small area by touch through rubber glove, without visual aid; therefore it would not be surprising if there were an error of as much as 0.5 cm. in the estimation of the size of the mitral valve. Therefore no attempt was made in this series to assess the size of the mitral orifice to such a fine degree. At operation the patients were divided into 2 groups: patients whose mitral orifice was estimated to be less than 1.5 cm. across (critical and severe mitral stenosis), and patients with a mitral orifice greater than 1.5 cm. across (mild or minimal stenosis).

The degree of mitral incompetence also has been assessed by Goodwin et al.[6] They divided their patients into 3 groups: patients in whom the mitral incompetence was described as an unimportant minimal regurgitant puff, patients in whom it was a moderate stream, and patients in whom the regurgitant stream was strong enough to hit the opposite wall of the atrium. Here again, the regurgitant stream was appreciated as a subjective sensation and the assessment of such a sensation must vary from surgeon to surgeon. Furthermore, the quantity of blood regurgitating and the force exerted by the stream, and so the intensity of sensation at the fingertip, must vary, not only with the size of the orifice, but with the force developed in the left ventricle during systole. This, in the main, depends on the degree of filling of the ventricle and it is known that, with the patient anesthetized, the chest open, and respiration maintained by positive pressure inflation, the cardiac output is reduced. This low output is reflected by the usually low systolic blood pressure of 60 to 80 mm. Hg observed during operations with the chest open. Thus it would seem that the estimation of the degree of mitral incompetence, to some extent, must be inaccurate and it has only been considered here under 2 headings, "unimportant" and "important."

RESULTS

The records of 156 patients were grouped according to their clinical and operative diagnoses. Briefly, 26 patients had no operation; 7 patients were not operated upon because their left atrial pressures were low, 2 because they were unfit as a result of other illness, 4 because of severe associated lesions of the heart, and 13 because of severe mitral incompetence. It is impossible to say how much the decision not to operate in this last group was influenced by the pressure record from the left atrium, but most certainly it was. These 26 cases were excluded from further consideration in this discussion.

In a further 5 patients a definite diagnosis could not be made at operation and these cases were also excluded from the following discussion.

The remaining 125 patients were divided into 2 groups, those with sinus rhythm and those with atrial fibrillation. In each of these 2 large groups the mitral lesion was assessed

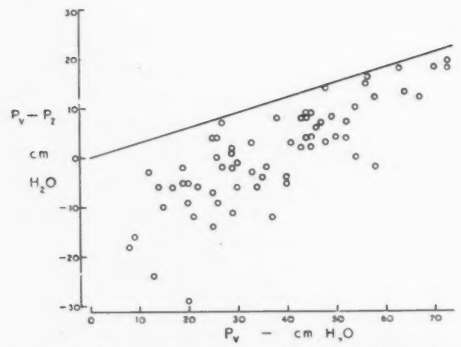

FIG. 2. Analysis of the records of left atrial pressure in patients who had mitral disease and whose hearts were in sinus rhythm. *Ordinate*, the difference between the pressure at the 'V' point and that at the 'Z' point (P_V-P_Z); *abscissa*, the pressure at the 'V' point (P_V). A line is drawn to indicate a 'mitral value' of 30. The open circles represent values from patients who had proved mitral stenosis at operation. No patient with sinus rhythm had severe regurgitation at operation.

clinically and at operation according to the described criteria.

The results of comparing the operative findings with the forecast obtained by calculating the "mitral value" from the pressure record are shown in diagrammatic form in figures 2 and 3. In figure 2 the difference between the pressure at the "V" point and at the "Z" point is plotted against the pressure at the "V" point, in patients with hearts in sinus rhythm. A line is drawn to indicate a "mitral value" of 30; above this number the value indicates the presence of regurgitation in patients in sinus rhythm. It shows that in this group, apart from about 4 patients with values just below the line, this method confidently predicted the presence of mitral stenosis severe enough to warrant operative treatment.

Figure 3 illustrates the measurements from the records of patients with atrial fibrillation; in this group the diagnosis cannot be made as accurately as in patients whose hearts are in sinus rhythm. Just below the line drawn to represent a "mitral value" of 50, above which patients are considered to have mitral incompetence, there are 6 values from patients with proved severe mitral stenosis. But because the "mitral value" was almost 50 in

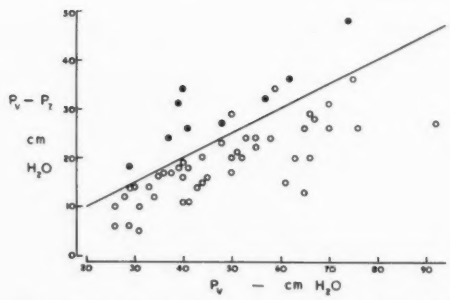

FIG. 3. Similar to figure 2; but the patients had atrial fibrillation and the line is drawn to indicate a 'mitral value' of 50. The open circles represent values from patients who had proved mitral stenosis at operation and the closed circles those who had severe regurgitation.

these 6 patients the diagnosis, based upon this value alone, was not made with confidence. In addition, 2 patients, observed to have mitral stenosis at operation each had a "mitral value" of 58 (shown as 2 open circles above the line in figure 3); one did have a calcified valve and a palpable regurgitant stream at operation but the lesion was mainly stenotic. No adequate explanation exists from the results in these 2 patients. Nevertheless the prediction of the diagnosis on a basis of the mitral value alone was wrong in only 2 patients.

The value of the method may be assessed in another way; in the following 13 patients the clinical diagnosis did not agree with the diagnosis made at operation, whereas in every case a prediction was made by means of the "mitral value." In figure 3 there are 9 points represented by closed circles above the line; at operation all these were proved to have a severe degree of regurgitation. All had "mitral values" of over 50 and because the hearts of these patients were fibrillating, these "mitral values" correctly predicted the diagnosis. But as a result of clinical and radiologic examinations 8 of these patients were said to have either a severe degree of pure mitral stenosis (3 cases) or a combined mitral lesion with predominant stenosis (5 cases). In addition in 3 patients, although the clinical and radiologic diagnosis of pure stenosis was severe enough for operative treatment, the left atrial pressure was within

the accepted range of normal (maximum pressure less than 20 cm. of water) and at operation there was minimal or mild stenosis. Lastly 2 patients were considered clinically to have combined stenosis and incompetence with the regurgitation predominant; both had pressure pulse contours that suggested mitral stenosis; and severe mitral stenosis was found at operation. One of these, a nursing sister, is a classical case in the department and has been quoted by Allison;[3] if it had not been for her own insistence on surgery, she would not have been operated upon. Her "mitral value" was 31 which, because of atrial fibrillation, clearly indicated stenosis, and at operation an uncomplicated tight stenosis was found and relieved.

Discussion and Conclusions

As long as there is no adequate operative procedure with which to alleviate the effects of mitral regurgitation, it is essential to distinguish preoperatively, as accurately as possible, between patients with stenosis and those with regurgitation. To this end any technic that increases the accuracy of diagnosis and limits the mistakes made, must be welcomed.

It is suggested that such a technic is that of recording the left atrial pressure through the bronchoscope; the attempt to predict the diagnosis solely from an examination of the pressure record was wrong in 2 patients, whereas a similar attempt by clinical and radiologic means was wrong in 13 patients out of a total of 125 patients. Also as a result of the interpretation of the left atrial pressure records, at least 11 patients out of 156 would rightly not have been operated upon if, with the experience possessed now, more attention had been paid to the pressure record and less to the clinical and radiologic diagnosis. Also examination of the left atrial pressure record suggested that no operation was necessary in 7 patients and helped to an unknown degree in weighing against operation in 13 patients who were considered to have severe mitral regurgitation. This empirical method is not infallible, and this is illustrated by the 2 patients whose left atrial pressure pulses predicted a major degree of regurgitation but who, at operation, had an operable degree of stenosis.

Since the first report of this empirical assessment[1] Morrow[8] has reported that this method of calculation from left atrial pressure records correctly predicted the diagnosis of mitral stenosis and regurgitation in patients with atrial fibrillation but the method was not so reliable when the heart was in sinus rhythm. However, by his modification of the technic of atrial puncture the zero was recorded at the level of the needle in the atrium, some 5 to 10 cm. below the manubrium sterni; all pressures measured on such a record would be 5 to 10 cm. of water greater than if they had been measured on a record obtained when the zero was level with the manubrium sterni. Thus "mitral values" calculated with the zero level 5 to 10 cm. below the manubrium sterni would give lower values and should not be compared with those presented in this report. The manubrium sterni zero level was deliberately chosen so that the "border line" between the values indicating stenosis and those indicating regurgitation could be set at 30 for patients in sinus rhythm and 50 for patients with atrial fibrillation.[1] Should it be desired to use a different zero level then it would be necessary to take a new "border line" obtained by assessing a large group of patients, or calculate it from the figures presented in this series.

Hutchison, Lawrie, and Thomson[9] have also had little success with this method. Detailed evidence on which this conclusion is based is not given. However their figure 5 (h) shows a record which, on their interpretation, suggested that gross mitral incompetence was present, but at operation the patient was found to have a tight mitral stenosis. In our opinion their interpretation of this record was wrong and the prediction from the record should have agreed entirely with their operative findings.

It is concluded that the examination of the left atrial pressure record is useful in patients with mitral disease, first to diagnose the lesion in those patients with mild or minimal stenosis (and this includes the patients followed post-

operatively because a maintained low left atrial pressure would indicate that there was no recurrence of severe stenosis) and second to distinguish between those patients with mitral stenosis and those with mitral regurgitation.

It must be emphasized that this method will only be of value if the limitations enumerated above are remembered and if in the original recording of the pressure contours attention is paid to the correct degree of needle damping, the absence of air bubbles in the system, the leveling of the manometer zero to, and only to, the manubrium sterni, and the correct measurement and interpretation of the records.

Summary

Some of the necessary conditions for the accurate recording of left atrial pressure by the bronchoscopic method are emphasized.

The records of 156 patients were examined and the patients placed in groups according to the clinical and radiologic diagnosis, the diagnosis at operation, and the diagnosis based only on an examination of the pressure record.

The attempt to predict the diagnosis solely from an examination of the pressure record was wrong in 2 patients only, whereas a similar attempt by clinical and radiologic means was wrong in 13 patients; out of a total of 125 cases.

It is concluded that in mitral disease this technic, used correctly, is useful to differentiate between stenosis and regurgitation and to distinguish those patients in whom the diseased mitral valve is not the main cause of the symptoms.

Acknowledgment

The patients were operated upon by Professor P. R. Allison, Mr. Goeffrey Wooler, Mr. John Alwyn, and one of us (A.J.G.). We are very grateful to Professor P. R. Allison for advice and criticism through this investigation.

Summario in Interlingua

Es signalate certes del conditiones necessari pro le accurate registration de pression sinistro-atrial per le methodo bronchoscopic.

Le dossiers de 156 patientes esseva examinate, e le patientes esseva organisate in gruppos secundo le diagnose clinic e radiologic, secundo le diagnose al operation, e secundo un diagnose basate exclusivemente super le examine del registration de pression.

Le essayo de predicer le diagnose exclusivemente super le base del examine del registration de pression succedeva mal in solmente 2 patientes. Un simile essayo super le base de solmente le datos clinic e radiologic succedeva mal in 13 patientes. Le total del casos in iste phase del studio esseva 125.

Es presentate le conclusion que in morbo mitral le technica bronchoscopic, si usate correctemente, representa un medio efficace pro differentiar inter stenosis e regurgitation e pro identificar le patientes in qui le morbide valvula mitral non es le causa principal del symptomas.

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Coexistence of Patent Ductus Arteriosus and Congenital Aortic Valvular Disease

By HERBERT MARK, M.D., BELLE JACOBSON, M.D., AND DENNISON YOUNG, M.D.

Congenital aortic or subaortic stenosis was demonstrated in 7 of 50 patients with patent ductus arteriosus. In addition to the murmurs characteristic of each lesion and diagnostic carotid artery pulse tracings, inordinate enlargement of the left ventricle with a small shunt through the patent ductus should suggest involvement of the aortic valve. The clinical findings associated with this combination of lesions are clear cut and awareness of them should lead to more frequent identification than has been reported previously.

PATENT ductus arteriosus is usually found as an isolated lesion in the patient with noncyanotic congenital heart disease. Infrequent reports of the co-existence of patent ductus arteriosus and aortic or subaortic stenosis have appeared in the literature.[1-4] We have encountered this combination of lesions in 7 of the first 50 patients operated on for patent ductus arteriosus. The purpose of this report is to indicate the criteria for clinical diagnosis in this group of patients.

Campbell and Kauntze,[5] Taussig and Schessel,[6] Grishman and associates,[7,8] Downing,[9] Young,[10] and others[11,12] have presented the clinical picture associated with isolated congenital lesions of the aortic valve. The criteria now appear to be well founded and generally accepted, despite a relative paucity of autopsy material. In the group of patients under consideration, because of the dynamic effects of the patent ductus arteriosus, these criteria require certain modifications.

CASE REPORTS

Case 1. A 14-year-old girl was admitted to the hospital in October 1950, with a diagnosis of congenital heart disease and healed bacterial endocarditis.

Examination revealed a systolic thrill and a loud harsh systolic murmur in the second right intercostal space that was transmitted to the neck vessels. In the second and third left intercostal spaces there was a loud, moderately long systolic murmur immediately followed by a short diastolic murmur. The aortic second sound was not heard. The blood pressure was 110/60 in the right arm and 160/88 in the right leg. There was no evidence of congestive failure.

The electrocardiogram showed a vertical heart and enlargement of the left ventricle with myocardial involvement. Angiocardiogram revealed marked hypertrophy of the left ventricle and the infundibulum of a ductus arteriosus.

Cardiac catheterization showed evidence of a patent ductus arteriosus. A direct brachial artery tracing was that of aortic or subaortic stenosis (fig. 1*C*).

At operation a patent ductus measuring 6 mm. long by 6 mm. wide was found. The aorta was extremely friable and tore at the site of the ductus insertion, and the patient died.

On postmortem examination the heart weighed 500 Gm. The left ventricle was markedly hypertrophied; the left atrium was slightly dilated and hypertrophied. The aortic valve ring measured 5.5 cm. in circumference. There was irregular diffuse thickening of all 3 aortic cusps on which were superimposed tiny white-yellow flecks. A thick rod of connective tissue ran along the bases of the cusps and fused with the cusps and endocardium resulting in stenosis of the outflow tract of the left ventricle (fig. 2). Microscopic examination showed thickening of the aortic cusps by moderately cellular connective tissue with a few scattered lymphocytes. The ductus showed no evidence of old or recent inflammation.

Comment. The patent ductus arteriosus was recognized by its characteristic murmurs, the aortic lesion by a different systolic murmur. Disproportionate left ventricular enlargement relative to the left-to-right shunt was believed to be due to the aortic valve lesion.

Case 2. A 5-year-old girl was admitted to Montefiore Hospital in April 1953. A heart murmur had been discovered at 1 month of age. Growth and development were normal.

On examination the heart was not enlarged. A continuous murmur and thrill were present in the

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second left intercostal space. In the second right intercostal space, however, the systolic murmur became rougher with transmission into the right carotid, and the diastolic murmur was of shorter duration and assumed a high pitched blowing character. The blood pressure was 80/40 in the left arm and 130/50 in the left leg. There was no congestive failure.

The electrocardiogram was normal. Cardiac fluoroscopy showed slight enlargement of the outflow tract of the left ventricle and slight enlargement of the left atrium. The pulmonary artery and hilar branches were slightly prominent. The supracardiac aorta and arch were mildly widened. The infundibulum of the ductus was readily visualized.

At operation a patent ductus arteriosus 4 mm. long by 5 mm. wide was found and ligated. Postoperatively the ductus murmurs disappeared and the blood pressure rose to 110/70. The harsh rough systolic murmur in the aortic area and short diastolic blow along the left sternal border persisted.

At present, 4 years later, the same murmurs are heard. The carotid artery pulse tracing is that of arotic or subaortic stenosis (fig. 1*B*). The patient continues well without cardiac symptoms. The electrocardiogram is normal and cardiac fluoroscopy shows no enlargement.

Comment. The patent ductus arteriosus was recognized by its characteristic murmurs, the aortic lesion by additional systolic and diastolic murmurs that were different in pitch, duration, and location. The aortic lesion apparently has no effect on cardiac dynamics.

Case 3. An 8-year-old girl was admitted to Montefiore Hospital in February 1955. A heart murmur had first been noted 6 months previously. Exertional dyspnea was the only complaint.

The heart showed no clinical enlargement. The pulmonic second sound was accentuated. In the second left intercostal space there was a long, loud systolic murmur and a softer, high-pitched diastolic with transmission below the left clavicle A systolic thrill was present in the same area. In the second right intercostal space there was a fairly loud systolic murmur transmitted into the neck. The blood pressure was 105/75 in the left arm and 150/105 in the left leg. There was no congestive failure.

Cardiac fluoroscopy revealed slight lengthening of the outflow tract of the left ventricle, and slight enlargement of the left atrium. The electrocardiogram was normal.

Cardiac catheterization showed evidence of a left-to-right shunt. An aortogram demonstrated a patent ductus arteriosus and additional anomalies of the great vessels of the aortic arch.

The ductus was closed in March 1955, following which the murmurs in the second left intercostal space disappeared, but the moderately loud harsh systolic murmur transmitted to the neck vessels has persisted. The blood pressure is 90/50. The carotid artery pulse tracing is consistent with aortic or subaortic stenosis. The child is asymptomatic and has grown and gained weight.

Comment. The murmurs caused by the patent ductus arteriosus were somewhat atypical but still distinct from an additional systolic murmur originating in the aortic area. Corroboration was obtained by laboratory means prior to surgery. The aortic lesion apparently has no dynamic effect.

Case 4. A 6-year-old boy was admitted to Montefiore Hospital in September 1953. A heart murmur had been discovered at the age of 3 months.

On examination there was a systolic thrill in the second left intercostal space and over both carotid arteries. The pulmonic second sound was split and accentuated. A "machinery type" murmur was heard in the second left intercostal space. In the aortic area there was a harsh systolic murmur and an early diastolic blow that was different in character from that heard in the second left intercostal space. At the apex there was a systolic blow and short mid-diastolic roll. The blood pressure was 100/25-0. There was no congestive failure.

The electrocardiogram indicated enlargement of both left and right ventricles, with a delay in right ventricular conduction. Cardiac fluoroscopy showed moderate enlargement of the left ventricle and the left atrium, slight enlargement of the right atrium and inflow tract of the right ventricle, and marked enlargement of the outflow tract of the right ventricle. The aorta was slightly dilated and showed expansile pulsations. The hilar vessels were moderately prominent.

At operation a patent ductus measuring 2 mm. long by 8 mm. wide was obliterated. A direct aortic pressure curve taken at the time of operation was consistent with aortic or subaortic stenosis.

On subsequent follow-up there has been a significant increase in size and weight. The aortic systolic murmur radiating into the neck persists. The blood pressure is 100/65. Roentgenographic study shows a decrease in size of the left atrium but the other chambers, aorta and hilar vessels are unchanged. The electrocardiogram still shows left and right ventricular enlargement and also deep inversion of the T waves in all the precordial leads.

Comment. The patent ductus arteriosus was readily recognized by its characteristic murmurs and the aortic lesion by the different systolic and diastolic murmurs. Despite elimination of the

ductus, the heart remains considerably enlarged with progressive myocardial involvement as manifested by the inversion of the T waves in all precordial leads. It is assumed that the aortic valvular disease is sufficiently obstructing to have increased the cardiac burden.

Case 5. A 12-year-old boy was admitted to Montefiore Hospital in August 1955. A heart murmur was first noted at 3 years of age. He had no cardiovascular symptoms.

Examination revealed the heart enlarged to the left. The pulmonic second sound was accentuated. A systolic thrill was felt in the second left intercostal space and in the suprasternal notch, and a continuous murmur was heard in the second left intercostal space. In the second right intercostal space the systolic and diastolic murmurs were separate and not continuous, the former being rough and the latter a high-pitched blow. The systolic component was also heard in the neck vessels. A systolic blow and a short diastolic roll were heard at the apex. The blood pressure was 130/26. There was no congestive failure.

The electrocardiogram showed a large left ventricle with inversion of the T wave in lead V_6. Roentgenographic study showed moderate enlargement of the left ventricle and slight enlargement of the left atrium and right ventricle. Both the aorta and the hilar vessels were moderately dilated and showed intrinsic expansile pulsations.

On cardiac catheterization a left-to-right shunt due to a patent ductus was demonstrated. At operation a patent ductus measuring 4 mm. long by 9 mm. wide was ligated. Following surgery the continuous murmurs disappeared but the moderately long and loud aortic systolic murmur transmitted to the neck vessels persists.

Over a 2-year follow-up period he has grown and gained weight at a greater rate than prior to operation. The blood pressure is 120/76. By x-ray the heart size has diminished, there being now only mild left ventricular and slight left atrial enlargement, decrease in the pulmonary vasculature, and disappearance of the hilar dance and expansile aortic pulsations. The electrocardiogram shows a lowering of the QRS voltage in the left-sided chest leads and the T wave in lead V_6 is upright. The carotid artery pulse tracing is that of aortic or subaortic stenosis.

Comment. The patent ductus arteriosus murmurs were characteristic. The additional aortic lesion was apparent from the obviously different murmurs in regard to location, pitch, and lack of continuity throughout the cardiac cycle. The major dynamic effect was due to the patent ductus, for since its obliteration the heart size has decreased considerably and the inverted T wave in lead V_6 has returned to normal.

Case 6. A 22-year-old girl was admitted to Montefiore Hospital in December 1951, in congestive heart failure. A heart murmur had been discovered at the age of 3 years. In September 1948, at another hospital, she was found to have a loud continuous murmur in the second left intercostal space, blood pressure 110/50 and a phonocardiogram typical of a patent ductus arteriosus. In October 1948 a large patent ductus was ligated.

In November 1948, she developed subacute bacterial endocarditis, which was successfully treated with penicillin. Following this she developed aortic systolic and diastolic murmurs and a corroborative phonocardiogram distinctly different from the earlier record. Cardiac catheterization showed no evidence of a patent ductus. It was believed that she had developed bacterial endocarditis on a congenital aortic valve anomaly.

On examination a systolic thrill was felt in the third left intercostal space and in the right carotid artery. The pulmonic second sound was accentuated, the aortic absent. A loud, long rough systolic murmur and a long, loud early diastolic blow were heard maximally in the third left intercostal space next to the sternum. The blood pressure was 160 to 300 systolic and zero diastolic. The liver was enlarged 3 fingerbreadths below the right costal margin.

The electrocardiogram showed a large left ventricle with myocardial involvement. Marked enlargement of the left ventricle and a dilated expansile aorta were seen on fluoroscopy. The hilar branches of the pulmonary artery were moderately dilated but showed no hilar dance.

She was discharged following treatment for the congestive failure but was rehospitalized 5 times in the subsequent 4 years because of this and anginal pain. The clinical findings were essentially the same. In 1954 cardiac catheterization was again performed and no shunt was demonstrable. In April 1956 she suddenly died at another institution.

Comment. This patient had a patent ductus arteriosus that was successfully obliterated but she developed bacterial endocarditis on an aortic valve anomaly, which resulted in severe deformity and possible rupture of a cusp. Dynamically, aortic insufficiency was the most important component.

Case 7. A 32-year-old woman was first admitted to Montefiore Hospital in May 1955, for treatment of subacute bacterial endocarditis.

On examination the heart was clinically enlarged. The fingers were clubbed. Congestive failure was present. The pulmonic second sound was accentuated. A systolic thrill was present in the pulmonic area, where a loud continuous "machinery-like" murmur was audible. In addition, a loud, harsh moderately long systolic murmur was

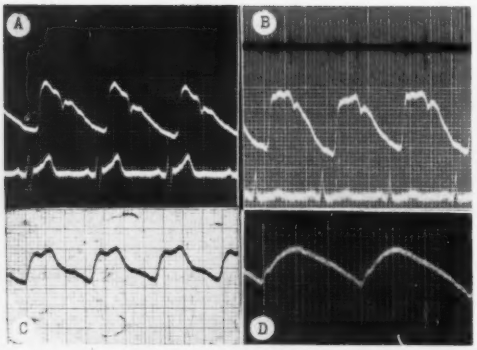

FIG. 1. Arterial pulse tracings. *A*. Normal. Systolic peak 0.08 second. *B*. Case 2. Plateau curve; delayed peak 0.20 second. "Diamond-shaped" murmur of aortic stenosis on phonocardiogram. *C*. Case 1. Direct brachial artery tracing. Double peak with systolic peak 0.26 second. *D*. Case 7. Low anacrotic notch. Systolic peak 0.22 second.

present in the aortic area and right carotid artery, and an early diastolic blowing murmur was heard in the third and fourth left intercostal spaces, adjacent to the sternum. The blood pressure was 120/70.

The electrocardiogram showed enlargement of the left ventricle. On cardiac fluoroscopy there was marked enlargement of the outflow tract of the left ventricle and slight enlargement of the left atrium and right ventricle; the lungs showed pulmonary congestion; the hilar branches were widened and showed intrinsic pulsations.

Following successful treatment of the bacterial endocarditis, operation was performed in July 1955, under induced hypotension. A patent ductus arteriosus measuring 4 mm. long by 8 mm. wide was ligated. Although the machinery murmur disappeared on the operating table, later that same day it was again heard. It was assumed that recanalization had occurred.

She was re-admitted in November 1955. Cardiac findings were the same as on the first admission, with no evidence of congestive failure. Cardiac catheterization was compatible with a patent ductus arteriosus. A carotid artery pulse tracing (fig. 1*D*) was that of aortic or subaortic stenosis.

At re-operation the patent ductus was divided. The aorta split at the upper margin of the insertion of the ductus and was repaired, but further bleeding later occurred and the patient died.

Comment. The patent ductus arteriosus was apparent by virtue of the typical murmurs. The murmurs representing an aortic lesion differed in their location and pitch from those associated with the patent ductus. The left-to-right shunt

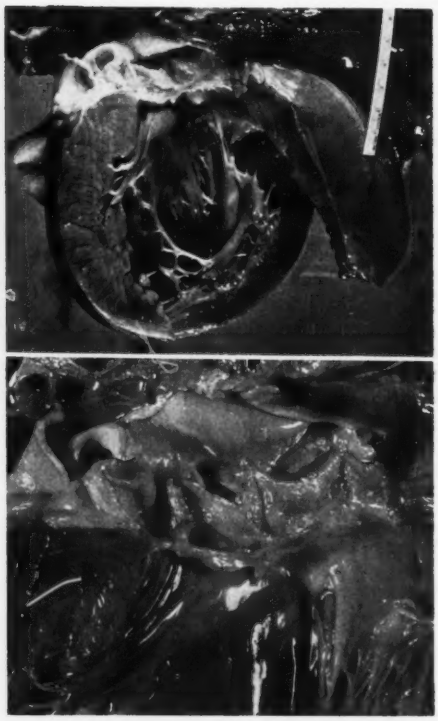

FIG. 2. Case 1. *Top*. Greatly hypertrophied left ventricular wall. *Bottom*. Higher magnification showing detail of the aortic valvular lesion. A thick band of tissue extends along the bases of the cusps and fuses with them.

through the ductus, as estimated by the pulse pressure and data obtained on cardiac catheterization, was small. The disproportionately enlarged left ventricle, therefore, was believed to be secondary to a significant degree of aortic obstruction.

DISCUSSION

Clinical recognition of the combined lesions is not difficult. The presence of a patent ductus arteriosus was readily determined by the classical continuous machinery murmur in the second left intercostal space with radiation to the left below the clavicle. This was confirmed at operation in each case. The diagnosis of an associated aortic valvular lesion was suggested prior to surgery in 5 patients. In a sixth, this was not recognized until after recovery from operation, and, in

the seventh, after operation performed at another hospital.

The aortic or subaortic valvular lesion was suspected when a separate systolic murmur, differing in quality and pitch from the systolic component of the continuous murmur, was heard in the second right intercostal space. This radiated into the neck and was sometimes associated with a thrill over the aortic area or the cervical vessels. In 4 patients additional early aortic diastolic blowing murmurs differing from the lower pitched diastolic murmur due to the patent ductus were heard. Transmission of the murmur to the neck preoperatively was not of diagnostic importance because this may also be noted in cases of uncomplicated patent ductus arteriosus. The aortic second sound was absent in only 1 patient of the 6 observed prior to surgery. Following obliteration of the patent ductus arteriosus, the continuous murmur disappeared. The loud, harsh, high-pitched aortic systolic murmur with radiation to the neck persisted in all, and a short early diastolic blow in one. In case 6 the aortic diastolic blow was not present preoperatively, but developed owing to the bacterial endocarditis.

Phonocardiography revealed a typical diamond-shaped murmur in some patients. The carotid artery pulse tracings[7, 8, 13] were studied in 4 patients, a direct aortic curve in 1, and in another a direct brachial artery curve was obtained (fig. 1). In our normal control group the peak came within 0.12 second of the onset of ejection, while it was delayed beyond 0.15 second in the presence of aortic stenosis. The clinical impression of aortic valvular disease was thus confirmed. We have not attempted to differentiate between aortic and subaortic stenosis on the basis of these studies.[12]

Four patients presented an electrocardiographic pattern of left ventricular enlargement. In another there was evidence of combined ventricular hypertrophy. The other 2 showed no abnormality.

All patients showed dilatation of the supracardiac segment of the aorta, a finding that has been considered significant in the diagnosis of isolated congenital aortic stenosis. It was of no diagnostic value in the present group of cases because of its frequent occurrence with patent ductus arteriosus. Roentgenographic evidence of cardiac chamber enlargement was in agreement with the electrocardiographic findings.

The width of the ductus at the time of operation was not unusually large in any of these patients (table 1). In addition, the calculated size of the shunt through the patent ductus, as determined by cardiac catheterization, was small in most.

Two patients, (cases 1 and 7) with small shunts and only moderate sized ductuses showed a large degree of left ventricular enlargement roentgenographically. Although these were two of the older patients, the left ventricular enlargement was still greater than expected with a simple patent ductus arteriosus of the indicated size. It is suggested, therefore, that disproportionate enlargement

TABLE 1.—*Correlation of Heart Size and Approximate Shunt*

Case	Age	Sex	BP	PA-RV O_2 · i ference (volume %)	ECG	X-ray	Size of ductus* (mr. .)
1	14	F	110/60	2.1	LV	LV 3+	6 × 6
2	5	F	80/40	1.7	N	LV sl.	4 × 5
3	8	F	105/75	1.7	N	LV sl.	—
4	6	M	100/25–0	—	LV & RV	LV 2+ RV	2 × 8
5	12	M	130/36	3.6	LV	LV 2+	4 × 9
6	22	F	110/50	—	LV	LV 2+	—
7	32	F	120/70	1.4	LV	LV 3+	4 × 8

* Av. 7 mm.—10 mm. × 5 mm.—7 mm. (Taussig[14]).
PA, Pulmonary artery; RV, Right ventricle; LV, Left ventricle.

TABLE 2. — *Associated Congenital Anomalies in Seven Patients with Patent Ductus Arteriosus and Congenital Aortic Valve Lesion*

Case no.	Congenital anomaly
1	Sprengel's deformity
3	Microphtnalmos, left eye
	Congenital cataract, left eye
	Anomalies of great vessels
	(five arteries off aortic arch)
4	Bilateral congenital nerve deafness

of the left ventricle in a patient with a patent ductus arteriosus and a relatively small shunt may point to the co-existence of a dynamically significant aortic valvular lesion.

Right heart catheterization ruled out intracardiac shunts in 6 patients subjected to these studies. In none was a history of rheumatic fever obtained nor were findings of additional valvular lesions present. Because the occurrence of isolated aortic stenosis on a rheumatic basis in children and young women is extremely rare, the aortic lesions in every case were assumed to be congenital in origin.

Three of these patients also demonstrated significant noncardiac congenital anomalies (table 2). This frequent association of anomalies has been noted by Bonham-Carter[2] in patients with patent ductus arteriosus and aortic valvular lesions. On the other hand, they are relatively infrequent in cases of uncomplicated patent ductus arteriosus.

Subacute bacterial endocarditis and sudden death are well known complications in patients with congenital lesions of the aortic valve. Three of these patients (cases 1, 6, 7) developed subacute bacterial endocarditis. Autopsy study of 1 patient revealed healed bacterial endocarditis of the congenital stenosed aortic valve and not of the ductus. In another patient, as well as could be determined at surgery, the ductus had not been the site of the previous bacterial endocarditis, and the third patient ultimately died with severe congestive heart failure following rupture of an aortic valve cusp.

The surviving 4 patients have now been followed 4, 2, 3½ and 2½ years since obliteration of the ductus. Two patients (cases 2, 3) show normal heart size and, therefore, the aortic lesion would seem to be of no dynamic significance. The other 2, however, (cases 4, 5) continue to show roentgenographically disproportionate left ventricular enlargement and case 4 shows additional electrocardiographic evidence of increasing ventricular "strain." It is assumed that in these 2 patients the aortic stenosis is of sufficient severity to overburden the heart even after elimination of the left-to-right shunt.

In such patients the possibility of an additional procedure, aortic commissurotomy, should be considered. In this regard, it might be advisable to obtain direct measurement of the pressure gradient across the aortic valve at the time of division of the ductus to estimate more accurately the degree of valvular obstruction.

SUMMARY

The co-existence of patent ductus arteriosus and congenital aortic or subaortic valvular disease is probably greater than has been previously noted. This combination has been found in 7 of 50 patients with proved patent ductus arteriosus. Relatively simple clinical criteria are presented for recognition of the combined lesions. In the uncomplicated patent ductus arteriosus one can be reasonably sure of cure following surgical obliteration. The prognosis cannot be as good when there is an associated aortic valve lesion with its attendant hazards of subacute bacterial endocarditis, increasing burden on the left ventricle, and sudden death.

ADDENDUM

Since submission of this paper, out of the next 40 patients with patent ductus arteriosus, we have seen 2 more with associated aortic valvular disease. This would make the incidence 10 per cent.

The first patient was a 5-year-old boy with clinical and laboratory evidence of a combined lesion. Six months after obliteration of the patent ductus arteriosus, his heart size has returned to normal. It is assumed, therefore, that the aortic lesion is dynamically unimportant at this time.

The second patient was a 20-year-old girl known to have a patent ductus since the age of 6 months. She had been carefully followed and always known to have no cardiac enlargement; the blood pres-

sures were about 120/80. She was seen by us 2 months after a healed bacterial endocarditis and found to have aortic insufficiency, a blood pressure of 110/0 and left ventricular and left atrial enlargement. Cardiac catheterization showed a relatively small shunt through a patent ductus. An aortogram showed aortic insufficiency and a bicuspid aortic valve as well as the patent ductus. This is most likely now a dynamically significant aortic insufficiency resulting from bacterial endocarditis of a bicuspid valve in the presence of a dynamically insignificant patent ductus arteriosus.

Summario in Interlingua

Le coexistentia de patente ducto arteriose con congenite morbo de valvula aortic es probabilemente plus frequente que previemente notate. Le combination esseva trovate in 7 ex 50 casos de demonstrate patente ducto arteriose. Es presentate relativemente simple criterios clinic pro le recognition del combinate lesion. In casos de non-complicate patente ducto arteriose on pote esser relativemente secur de curation post oblitteration chirurgic. Le prognosis non pote esser equalmente bon in casos de associate lesiones del valvula aortic proque istos adde le hasardos de subacute endocarditis bacterial, de augmentate cargas sinistro-ventricular, a de morte subitanee.

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Biosynthesis of Epinephrine and Norepinephrine by Sympathetic Nerves and Ganglia

By McC. Goodall, M.D., Ph.D., and Norman Kirshner, Ph.D

It is generally believed by the neurophysiologists that the sympathetic neurohormone is norepinephrine and not epinephrine as originally supposed. This concept of norepinephrine as the sympathetic neurohormone has evolved from much impressive circumstantial evidence; however, it has not been demonstrated that the biosynthesis of norepinephrine takes place in the sympathetic nerves and ganglia. This paper shows, through the use of labeled precursors, that the sympathetic nerves and ganglia synthesize norepinephrine in a systematic sequence from tyrosine and that this synthesis apparently terminates with norepinephrine rather than progressing to the formation of epinephrine.

THE neurohormone of the sympathetic nerves is now generally accepted as being norepinephrine.[1-7*] Norepinephrine is also found in the adrenal medulla but in most mammals the amount of norepinephrine is considerably less than the amount of epinephrine.[3, 8] The neurohormone of the parasympathetic nerves is acetylcholine; however, it appears that many parasympathetic nerves also contain adrenergic fibers.[3, 9]

Recent evidence indicates that the biosynthetic pathway to epinephrine and norepinephrine formation is via dihydroxyphenylalanine and hydroxytyramine,[10, 11] (fig. 1). Goodall and Kirshner[11] showed that bovine adrenal slices incubated with tyrosine uniformly labeled with C^{14} produced in sequence: hydroxytyramine, norepinephrine, and epinephrine. Further, they showed that when C^{14} dihydroxyphenylalanine (dopa) was incubated with bovine adrenal homogenates, hydroxytyramine, norepinephrine, and epinephrine were synthesized in that order. Gurin and Delluva[12] and Udenfriend and Wyngarden[13] isolated radioactive epinephrine from rat and rabbit adrenal glands after intraperitoneal injection of C^{14} labeled tyrosine; however, they did not show the sequence of this conversion.

Hitherto, no one has shown whether sympathetic and parasympathetic nerves are capable of synthesizing epinephrine and norepinephrine. Albeit, Euler [1-3] has shown that the sympathetic nerves, and to a much less degree some parasympathetic nerves, contain small amounts of epinephrine and comparatively large amounts of norepinephrine. Holtz and Westermann[14] have shown that the sympathetic and vagus nerves contain dopa decarboxylase. Schümann[15] has demonstrated the presence of hydroxytryramine in extracts of sympathetic nerves, and others[6, 7] have shown that the sympathetic nerves release norepinephrine.

Method

Dogs were anesthetized with Nembutal and killed by bleeding. The splenic nerves, the thoracic sympathetic nerves, the thoracic sympathetic ganglia, and the cervical vagi were immediately removed. In order to compare the result obtained from one species of mammal with that of another, similar nerves and ganglia were obtained from beef immediately after slaughtering.

Approximately 0.10 to 0.20 Gm. of each of these nerve groups were minced with scissors and incubated. A gas mixture of 95 per cent oxygen and 5 per cent carbon dioxide was bubbled through the medium during the incubation period. Each incubation contained 10 μmoles of glucose, 50 μg. of pyridoxal phosphate, 1 μmole of adenosine tri-

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Supported by U. S. Public Health Service grant H-2546.

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*The authors prefer the terms adrenaline and noradrenaline rather than epinephrine and norepinephrine but have been agreeable in this instance to conform to our current editorial usage.—*Ed.*

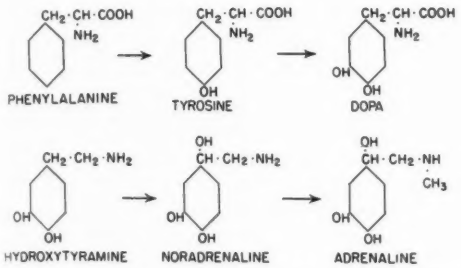

FIG. 1. Biosynthetic pathway to epinephrine and norepinephrine.

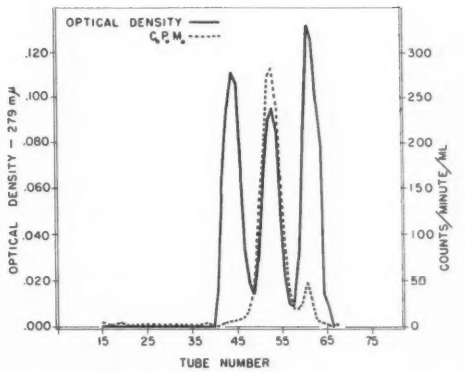

FIG. 2. Separation of epinephrine, norepinephrine, and hydroxytyramine from an incubation of sympathetic nerves and C^{14}-labeled tyrosine. Dotted lines indicate the incorporation of radioactivity in the norepinephrine and hydroxytyramine fractions. From left to right, the peaks represent epinephrine, norepinephrine, and hydroxytyramine. Experimental conditions described under table 2.

phosphate, 0.5 μmole of diphosphopyridine nucleotide, and 1×10^6 c.p.m. of uniformly labeled tyrosine with a specific activity of 7.7 mc. per mM, or 4.5×10^5 c.p.m. of dl-dihydroxyphenylalanine-2-C^{14} with specific activity of .835 mc. per mM. Extracts of the nerves were then prepared by adding 0.2 volumes of 50 per cent trichloroacetic acid to the incubation medium. The precipitate was removed by filtration and washed with 5 per cent trichloroacetic acid. The filtrate and washings were combined and extracted 3 times with an equal volume of ether to remove the trichloroacetic acid.

In accordance with the procedure described by Kirshner and Goodall,[18] a preliminary purification of the extract was obtained by ion exchange on a 2.5×0.9 cm. column of Amberlite IRC-50. The pH of the extract was adjusted to 6.1 to 6.3 and 200 μg. each of nonlabeled hydroxytyramine, norepinephrine, and epinephrine were added as carriers. The extract was placed on the Amberlite column and allowed to run through at a flow rate of approximately 1 ml. per minute. The resin was then washed 3 times with 3-ml. portions of distilled water and the catechol amines were eluted with three 5-ml. portions of 2.0 N acetic acid. The

TABLE 1.—*Formation of Epinephrine, Norepinephrine and Hydroxytyramine from Dopa 2-C^{14} and from C^{14} Uniformly Labeled Tyrosine by Canine Nerves*

Type of nerve tissue	Number of experiments	Counts per minute per 0.1 Gm. tissue		
		Epinephrine	Norepinephrine	Hydroxytyramine
Dopa-2-C^{14}				
Splenic sympathetic nerve	5	16 ± 4	247 ± 183	9,485 ± 10,860
Thoracic sympathetic nerve	5	20 ± 20	153 ± 116	7,453 ± 5,000
Stellate ganglia	5	10 ± 3	186 ± 154	10,470 ± 5,260
Vagus—cervical	4	5 ± 3	13 ± 12	954 ± 1,403
Boiled sympathetic nerve	4	6 ± 7	6 ± 3	18 ± 7
Tyrosine-C^{14}				
Splenic sympathetic nerve	4	35 ± 20	165 ± 90	39 ± 7
Thoracic sympathetic nerve	4	62 ± 38	424 ± 227	70 ± 43
Stellate ganglia	4	41 ± 32	205 ± 89	81 ± 34
Vagus—cervical	4	17 ± 19	22 ± 16	17 ± 20
Boiled sympathetic nerve	4	28 ± 17	13 ± 9	15 ± 15

Each incubation contained 1 μmole adenosinetriphosphate, 0.5 μmole of diphosphopyridine nucleotide, 10 μmoles of glucose, 50 μg. of pyridoxal phosphate, 2 ml. Kreb's phosphate buffer[21] pH 7.4, 0.1 to 0.2 Gm. of the minced tissue and either dl-dopa-2-C^{14} (4.5×10^5 c.p.m., SA = 0.835 mc./mM) or C^{14} uniformly labeled l-tyrosine (8.0×10^5 c.p.m., SA = 7.7 mc./mM). Final volume was 3.0 ml. Incubation time was 3 hours with dopa and 6 hours with tyrosine at 37°.

ammonium acetate and the acetic acid were removed *in vacuo* at 35°.

The catechol amines in the extract were then fractionated by column chromatography. The residue was dissolved in 2.0 ml. of 0.2 M ammonium acetate buffer pH 6.1 A 1-ml. aliquot of the above referred solution was placed on a 30 by 0.9-cm. column of Amberlite IRC-50 followed by 1.0 ml. of 0.2 M ammonium acetate buffer pH 6.1. The column was then connected to a reservoir of 0.4 M ammonium acetate buffer pH 5.0. The flow rate was adjusted to 3.5 to 4.0 ml. per hour; fractions of 1.5 ml. were collected.

The amounts of epinephrine, norepinephrine, and hydroxytyramine in each fraction were determined by measuring the optical density at 279 μ. All fractions containing the same catechol amines were pooled and evaporated to dryness *in vacuo* at 35°. The residue was dissolved in water and an aliquot plated out for measuring the radioactivity. Radioactivity was measured with a thin window flow counter that had an average background of 16 c.p.m. The data presented have been corrected for background radioactivity

Results

Dihydroxyphenylalanine (dopa) Incubation

Tables 1 and 2 are tabulations of the radioactivity found in the epinephrine, norepinephrine, and hydroxytyramine fractions after incubating the various nerve groups with C^{14}-labeled dihydroxyphenylalanine (dopa). From these tables, it appears that the sympathetic nerves and ganglia synthesize hydroxytyramine and norepinephrine from dopa. However, the radioactivity in the epinephrine fraction was so low that it was not feasible to purify the material further and thereby to eliminate the possibility of contamination.

The vagal nerves are also capable of synthesizing hydroxytyramine from dopa; however, the radioactivity found in the hydroxytyramine fractions is far less than that found in similar fractions obtained from the sympathetic nerves and ganglia. The vagal nerves do not appear to synthesize epinephrine or any appreciable amounts of norepinephrine.

Tyrosine Incubation

Tables 1 and 2 are tabulations of the radioactivity found in the epinephrine, norepinephrine, and hydroxytyramine fractions after

TABLE 2.—*Formation of Epinephrine, Norepinephrine and Hydroxytyramine from Dopa-2-C^{14} and from C^{14} Uniformly Labeled Tyrosine by Bovine Nerves*

Type of nerve tissue	Number of experiments	Counts per minute per 0.1 Gm. tissue		
		Epinephrine	Norepinephrine	Hydroxytyramine
Dopa-2-C^{14}				
Thoracic sympathetic nerve	1	11	603	16,000
Thoracic sympathetic ganglia	1	12	317	23,360
Stellate ganglia				
3 hr. incubation	1	29	332	39,400
6 hr. incubation	2	8 ± 2	149 ± 25	590 ± 476
Cervical sympathetic nerve	1	8	27	900
Vagus—cervical	1	4	9	500
Tyrosine-C^{14}				
Thoracic sympathetic nerve	3	16 ± 7	417 ± 158	73 ± 31
Thoracic sympathetic ganglia	3	13 ± 7	653 ± 270	94 ± 23
Stellate ganglia				
6 hr. incubation	3	14 ± 7	763 ± 458	107 ± 48
Cervical sympathetic nerve	1	6	70	33
Vagus—Cervical	2	10 ± 3	12 ± 1	4 ± 1
Boiled sympathetic nerve	2	2 ± 3	4 ± 1	2 ± 1

Each incubation contained 1 μmole of adenosine-triphosphate, 0.5 μmole of diphosphopyridine nucleotide, 10 μmoles of glucose, 50 μg. of pyridoxal phosphate, 2 ml. of Kreb's phosphate buffer[21] pH 7.4, 0.1 to 0.2 Gm. of the minced tissue and either dl-dopa-2-C^{14} (4.5×10^5 c.p.m., SA = 0.835 mc./mM), or C^{14} uniformly labeled l-tyrosine (7.8×10^5 c.p.m., SA = 16.3 mc./mM). Final volume was 3.0 ml. Incubation time was 3 hours with dopa and 6 hours with tyrosine at 37°.

incubating the various nerves and ganglia with uniformly labeled tyrosine. From these tables it appears that the sympathetic nerves and ganglia synthesize hydroxytyramine and norepinephrine; however, from this data it is again impossible to conclude whether or not epinephrine is formed. Figure 2 presents the results obtained from incubating bovine thoracic sympathetic chain with labeled tyrosine. Here the radioactivity and the optical density are plotted against the fraction numbers.

The radioactivity of the hydroxytyramine fraction formed by incubating dopa with sympathetic nerves and ganglia was greater than the radioactivity of the hydroxytyramine fraction formed by incubating with tyrosine. This is because the conversion from dopa to hydroxytyramine is rapid, while that from tyrosine to dopa is slow.

The vagal nerves appear incapable of synthesizing epinephrine, norepinephrine or hydroxytyramine from tyrosine. This would then lead one to believe that cholinergic nerves *do not* normally synthesize norepinephrine.

General Results

The results presented in tables 1 and 2 are calculated on the basis of counts per minute per 0.1 Gm. of tissue; however, from the specific activity of the tyrosine and dopa, and from the amount of radioactivity in the norepinephrine fraction, the absolute amounts of norepinephrine found after the incubations have been calculated. With dog sympathetic nerves and ganglia, the average total amount found after a 3-hour incubation with dopa was 0.51 ± 0.39 μg; after a 6-hour incubation with tyrosine the average total amount found was 0.072 ± 0.066 μg. With bovine sympathetic nerves the average total amount found after a 3-hour incubation with dopa was 1.08 μg, and after a 6-hour incubation with tyrosine the amount found was 0.078 ± 0.036 μg. The amounts of norepinephrine found are the differences between the amounts synthesized and the amounts destroyed by monoamine oxidase, possibly other enzymes and by chemical oxidation. That this destruction is considerable can be seen from table 2, in which the amounts of norepinephrine found after a 6-hour incubation of the stellate ganglia with dopa is less than one half the amount found after a similar 3-hour incubation. Previous work on the formation of epinephrine and norepinephrine from tyrosine in the adrenal medulla [11] indicated that maximum norepinephrine formation was found after a 6-hour incubation.

Dopa and Tyrosine Incubated with Marsilid

Sympathetic nerves were incubated with dopa and Marsilid. Results of these experiments showed an increase in the radioactivity of the hydroxytyramine fraction. In that Marsilid is a monoamine oxidase inhibitor,[3] it inhibits oxidation of hydroxytyramine and thereby apparently permits hydroxytyramine to accumulate. This is less apparent when it is incubated with tyrosine, since the conversion from tyrosine to dopa is slow. [11]

Discussion

Epinephrine has long been known to be present in the adrenal gland[17, 18] and for many years was thought to be the neurohormone of the sympathetic nerves. However, as early as 1910 Barger and Dale [19] questioned the validity of epinephrine as the sympathetic neurohormone. In 1946 Euler [1] showed that the sympathetic nerves contained predominately norepinephrine. Recent work[1-7] supports Euler's concept of norepinephrine as the sympathetic neurohormone.

Hitherto, there has been little evidence indicating the biosynthetic pathway of norepinephrine formation in adrenergic nerves, although it would seem that the pathway should be identical with that in the adrenal gland. [11] Experiments herein described show that the sympathetic nerves and ganglia incubated either with tyrosine or dopa synthesized hydroxytyramine and norepinephrine, but only questionable amounts of epinephrine. Therefore, it appears that the same biosynthetic pathway does occur in the sympathetic nerves and ganglia as in the adrenal medulla[11] (fig.

1). However, since the amount of epinephrine formed by the nerves was hardly detectable, one could only conclude that if epinephrine is synthesized, the rate of synthesis is significantly slow. In contrast the norepinephrine was readily detected and significantly high. Therefore, it seems reasonable that the neurohormone of the sympathetic nerves is norepinephrine, and that epinephrine, if present, is of questionable importance in sympathetic nerve transmission.

Also from the experiments herein described, it appears that the vagus nerve is incapable of synthesizing epinephrine or norepinephrine from tyrosine or dopa. However, some slight radioactivity noted in the hydroxytyramine fraction after incubation with dopa, would indicate that the vagus nerve could synthesize hydroxytyramine. Euler[2, 3, 20] showed that the vagus nerve contained small but definite amounts of norepinephrine and found that this was highly suggestive of the presence of adrenergic fibers within the vagus. The absence of radioactive norepinephrine in the vagus nerve incubation experiments probably means that the amount of radioactive norepinephrine formed was so small that its detection was inconclusive. Therefore, it would seem that cholinergic nerves do not synthesize epinephrine or norepinephrine, but if they do, the quantity formed is significantly small.

Summary

With the use of labeled precursors, the biosynthesis of epinephrine and norepinephrine by sympathetic ganglia and nerves and parasympathetic nerves was studied. Sympathetic nerves and ganglia incubated with either labeled tyrosine or labeled dihydroxyphenylalanine formed radioactive hydroxytyramine and norepinephrine. The vagus nerve incubated with either labeled tyrosine or labeled dihydroxyphenylalanine formed no significant amounts of radioactive epinephrine or norepinephrine and only small amounts of radioactive hydroxytyramine. The evidence presented supports the concept that norepinephrine is the neurohormone of the sympathetic nerve.

Summario in Interlingua

Per medio del marcation del precursores de epinephrina e norepinephrina, le biosynthese de iste substantias in gangliones e nervos sympathic e in nervos parasympathic esseva studiate. Nervos e gangliones sympathic incubate con tyrosina marcate o con dihydroxyphenylalanina marcate formava radioactive hydroxytyramina e norepinephrina. Le nervo vage incubate con tyrosina marcate o con dihydroxyphenylalanina non formava significative quantitates de radioactive epinephrina o norepinephrina e solmente parve quantitates de radioactive hydroxytyramina. Es supportate le conception que norepinephrina es le neurohormon del nervo sympathic.

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The 8 patients described in this paper have 3 features in common: all of them developed shock in the terminal phases of their illnesses, all 8 were treated vigorously with levarterenol (Levophed), and diffuse damage involving the proximal tubules associated with changes in the glomeruli and blood vessels were present. These lesions in the kidney are similar to the "proximal tubular necrosis" with "focal cortical necrosis" described by Sheehan and Moore and attributed by them to vasospasm. It is therefore suggested that the postmortem findings with respect to the kidneys, in the 8 patients described in this report, are the result of severe ischemia due to spasm of the renal arterioles and the medullary veins. The cause of the spasm is believed to be shock which was intensified and prolonged by the therapy with levarterenol.

Wendkos

Coronary Arteriovenous Fistula

By Israel Steinberg, M.D., Janet S. Baldwin, M.D., and Charles T. Dotter, M.D.

Angiocardiography and physical findings established the diagnosis of a coronary arteriovenous aneurysm in a 6-year-old asymptomatic schoolgirl. During the 7 years that have ensued, her heart size, electrocardiogram, and general condition have remained normal. Review of the literature discloses 13 autopsy-proved coronary artery fistulas and 8 cases wherein the diagnosis was established by exploratory thoracotomy or cardiac catheterization. The data indicate a wide variation in the clinical significance of the lesion and lead to the conclusion that management is best established on an individual basis.

ABNORMAL communications between coronary arteries and the coronary venous system constitute arteriovenous lesions in the strictest sense of the word. To use the term arteriovenous with reference to communications between the coronary arteries and structures such as the right atrium, right ventricle, and the pulmonary artery is open to criticism from a semantic point of view, but appears to have become accepted through common usage. In this report, arteriovenous refers to any fistulous communication through which blood is shunted into vascular channels without first passing through capillaries. Although all coronary fistulas exhibit dilatation usually aneurysmal in degree, the converse is not true (i.e., not all coronary aneurysms are due to fistulas). Coronary arteriovenous fistulas are potentially serious lesions that have been successfully treated surgically; their diagnosis is, therefore, a matter of concern to all physicians. Thirteen of 21 previously reported coronary arteriovenous fistulas were revealed at autopsy and in 8 additional cases the diagnosis was established during life by thoracotomy or cardiac catheterization.[1-23] In the case to be described, a continuous high-pitched "superficial" murmur, best heard to the left of the lower sternum, suggested the presence of an arteriovenous fistula while angiocardiography demonstrated aneurysmal dilatation of a coronary vessel.

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Aided by grants from Mallinckrodt Chemical Works.

Case Report

A 6-year-old schoolgirl was referred for consultation in May 1949 because of a heart murmur first heard a year previously. The medical history indicated that her birth followed a normal pregnancy and that physical development and functional capacity had been normal. Under medical observation she has continued to develop normally to her present age of 13 years. She has always been an energetic child, participating in all ordinary childhood activities save for highly competitive sports.

On physical examination, abnormal findings were limited to the heart and have shown no significant change during the 7-year period of observation. The pulse and apex beat were normal. A thrill was not detected. The intensity of the heart sounds was unremarkable. Normal duplication of the second sound in the pulmonary area was observed with the patient in the supine position. A striking cardiac murmur was present. This murmur was loudest in the left fourth and fifth interspaces at the midclavicular line, less intense at the left sternal border, and faintly audible at the angle of the left scapula. It was not transmitted into the axilla. A peculiar superficial quality was noted by all observers. The murmur, moderately high pitched and hollow in quality, began late in systole while its greatest intensity occurred during early diastole, throughout which phase it was continuous (fig. 1). The intensity became markedly accentuated during expiration. Blood pressure in the arms was 106/72 mm. Hg; in the legs, 115/80.

Roentgenographic examination of the heart, electrocardiographic studies and functional tests were negative and have remained so.

Prior to angiocardiography, the diagnosis of arteriovenous fistula involving diaphragmatic or anterior chest wall vessels was suspected because of the location, late onset, and very superficial quality of the continuous murmur. Angiocardi-

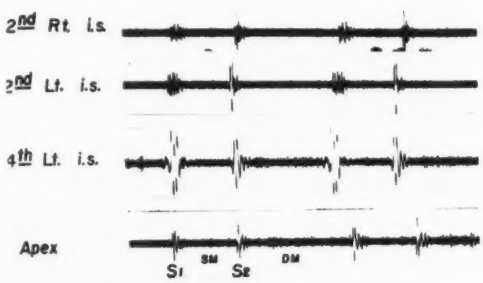

FIG. 1. Stethogram showing maximum focus of the continuous murmur at fourth left interspace. Note accentuation throughout mid and late third of diastolic phase. (Tracing courtesy of Dr. J. Scott Butterworth.)

ography (figs. 2, 3), performed January 10, 1952, revealed a tortuous, markedly dilated vessel or group of vessels apparently located in the anterolateral wall of the heart and filling simultaneously with the ascending aorta. Film detail was impaired by patient movement, and it was consequently impossible to delineate with certainty the proximal portion of the involved coronary artery, apparently the right, or the site of the abnormal communication. Considered together, however, the angiocardiographic and physical findings are regarded as diagnostic of a coronary arteriovenous fistula with aneurysmal dilatation of the shunt-bearing vessels. The late onset and maximum diastolic intensity of the murmur are consistent with shunting during the diastolic period of coronary blood flow; the area of maximum intensity and superficial quality of the murmur are consistent with the course of a coronary artery.

During the 7-year period of observation, there has been no disproportionate increase in heart size. Physical development and functional capacity remain excellent. It is planned to continue this patient's medical observation on a routine basis. Should there be subsequent appearance of symptoms or functional disability, surgery will be reconsidered and in this event coronary arteriography and cardiac catheterization can be employed to achieve accurate anatomic and functional diagnoses.

REVIEW OF LITERATURE

Cases of coronary artery fistula have been included in published reports dealing with other types of coronary lesions, particularly aneurysms. In certain instances the published evidence suggests that abnormal communications were overlooked; in others, mention of arteriovenous fistula appears to have been incidental to the description of coronary aneurysms. This is putting the cart in front of the horse, since arteriovenous fistulas are an important cause of coronary aneurysm. Scott's recent review of coronary artery aneurysms[7] included 5 stated examples of abnormal communications in a total series of 48 aneurysms. A review of the literature on coronary aneurysm indicates that there has been a general failure to recognize the etiologic importance (and sometimes the presence) of arteriovenous fistulas in this condition.[24-29] Twenty-two cases of coronary arteriovenous fistula, briefly summarized in table 1, are reviewed in this report in order to demonstrate the features of this lesion. Except for case 22, our case, all were collected from previously published case reports. Certain cases purposely were not included in this review.

DESCRIPTION OF TWENTY-ONE PREVIOUSLY REPORTED CASES OF CORONARY ARTERIOVENOUS COMMUNICATIONS

Case 1. Abbott[1] in 1908 reported the findings in a 60-year-old woman who died accidentally; detailed data were not recorded. The left coronary artery took anomalous origin from the pulmonary artery and there was a "crab apple sized" dilatation of the right coronary artery close to its origin from the aorta, believed to be due to a communication with the anomalous left coronary artery. Abbott stated, "The course of blood was towards the pulmonary artery."

Case 2. Halpert[2] described a case of congenital arteriovenous fistula wherein a branch of the right coronary artery was aneurysmally dilated and communicated with the coronary sinus via an anastomotic loop that exhibited histologic characteristics of both arteries and veins. Aneurysmal, serpentine dilatation involved the structures through which the abnormally shunted blood passed; branches of the right coronary artery distal to the "feeder" branch were not remarkable. Although cardiac symptoms or signs were not known to have been present, the heart weighed 500 Gm. and the left ventricle was hypertrophied.

Case 3. Nagoya and Takahashi[3] described a marked, diffuse, serpentine aneurysmal dilatation of the circumflex branch of the left coronary artery that communicated directly with the coronary sinus (also dilated). Cardiac symptoms had been present for 10 years prior to death from myocardial

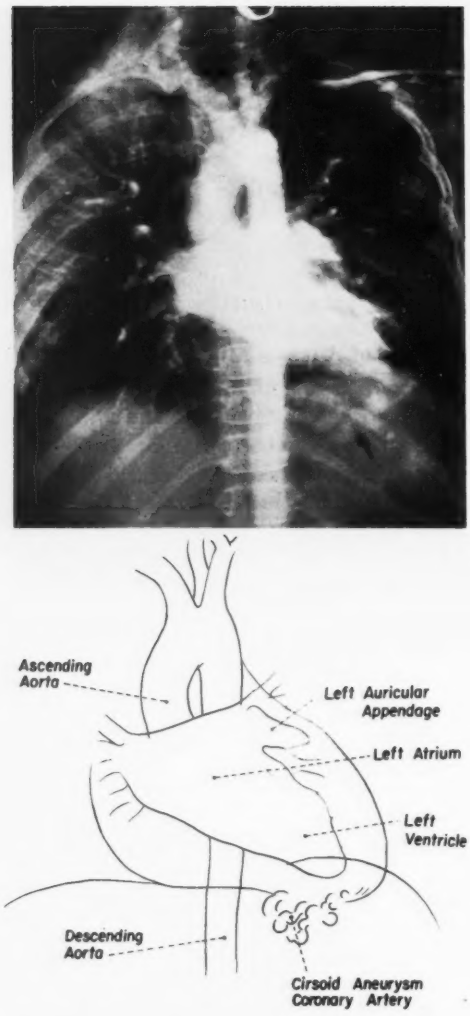

FIG. 2. Coronary arteriovenous fistula in an 8-year-old asymptomatic girl. *Top.* Frontal angiocardiogram showing the left atrium, left ventricle, and aorta. Below the left ventricle there is a cluster of large coiled vessels (arrow). *Bottom.* Tracing of top.

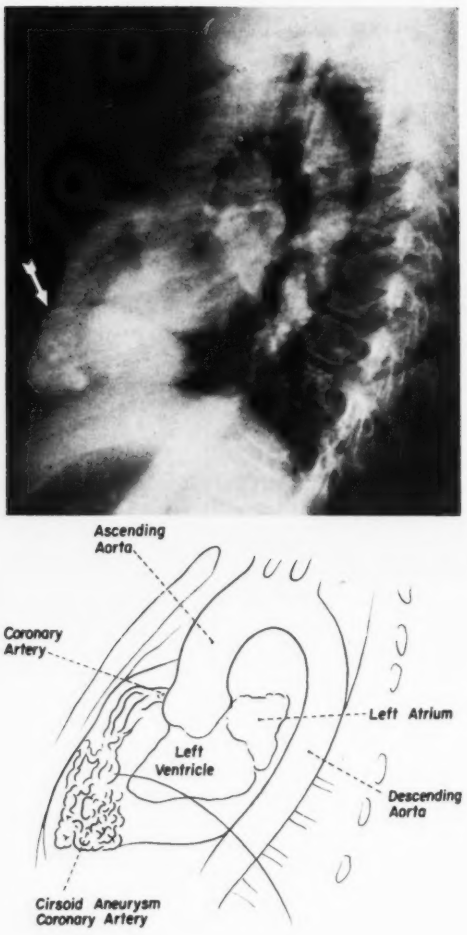

FIG. 3. Same case as figure 2. *Top.* Lateral angiocardiogram. Cirsoid, markedly dilated coronary vessels (*arrow*) fill simultaneously with the aorta and are shown near the apex of the heart. *Bottom.* Tracing of top.

infarction of their 72-year-old patient, and a murmur had been audible for many years.

Case 4. Löwenheim[4] found a right coronary arteriovenous fistula in a 62-year-old man who exhibited cardiac failure and hypertension (260/100 mm. Hg) for at least 2 years prior to death. At autopsy, the heart weighed 835 Gm. the left ventricle being markedly hypertrophied.

Case 5. Harris[5] reported the case of a 43-year-old man stated to have been free of cardiac symptoms (no clinical data were recorded save for the fact that death was due to cerebral hemorrhage). Autopsy revealed a diffuse, cirsoid aneurysmal dilatation of the right coronary artery that communicated with the right atrium through a 1-mm. opening. The heart weighed 380 Gm.

TABLE 1.—*Case Summaries*

TABLE 1.—*Case Summaries*

Age, race, sex	Reference, author, year (Diagnosis by)	Pathologic data	Clinical data			Remarks
			Blood pressure	Murmurs	Reported symptoms of cardiac disease	
Case 1 60 WF	Abbott[1] 1908 (Autopsy)	Dilated RCA → PA via anom. LCA. Aneurysm size of a "crab apple." Heart weight not stated	Not stated	None described	No	Accidental death
Case 2 54 WM	Halpert[2] 1930 (Autopsy)	Diffusely dilated RCA → dilated coronary sinus via interven. loop which had charac. of art. and vein. Heart weight = 500 Gm.	125/70	Systolic only	No	15 year history of intermittent painful arthritis. Enlarged heart. Atheroscler. of coronaries. Died of post-op. carcinoma of stomach.
Case 3 72 WM	Nagoya[3] 1932 (Autopsy)	LCA circumflex → coronary sinus. Diffuse serpentine dil. involved structures. Heart weight = ?	?	?	Precordial pain, palpitations, dizziness, dyspnea, cyanosis. "Puny in childhood."	Died of myocardial infarct
Case 4 62 WF	Lowenheim[4] 1932 (Autopsy)	RCA → R. coronary vein via "narrow" orifice. Walls thicken. Diffuse aneurysmal dilat. involved parts. Cardiac hypertrophy, esp. LV. Heart weight = 835 Gm.	260/100	None described	Increasing symptoms of heart failure for at least 2 years.	Died of heart failure
Case 5 43 WM	Harris[5] 1937 (Autopsy)	Branch of RCA → RA via 1 mm. orifice; diffuse cirsoid dil. of coronary sinus and involv. parts RCA. R. heart much dilated. Heart weight = 380 Gm.	Not stated	None described	No	Died of hemorrhage into brain tumor
Case 6 43 WF	Emminger[6] 1946 (Autopsy)	Diffusely dil. RCA → Great card. vein thru small orif. Coronary sinus → RA by 2 ostia; origin RCA = 1.4 cm. Heart weight not given	150/65	None described	Not recorded	Died of uremia due to glomerulonephritis
Case 7 84 WM	Scott[7] 1948 (Autopsy)	LDCA and anom. branch RCA → PA. 17 aneurysms of shunt-bearing arts. Non-shunt bear. coronaries normal. Largest aneurysm clotted. Heart weight = 780 Gm.	120/70	None described	No	Died of uremia with carcinoma of prostate. Clot in aneurysm may explain lack of murmur

* In living patients, age given at time diagnosis was estab*li*shed.

TABLE 1.—*Case Summaries—Continued*

Age, race, sex	Reference, author, year (Diagnosis by)	Pathologic data	Clinical data			Remarks
			Blood pressure	Murmurs	Reported symptoms of cardiac disease	
Case 8 1 NM	Brown[8] 1949 (Autopsy)	Accessory LCA → RV. Narrowest diameter was 5 mm. Heart weight not stated	98/65	Machinery	No	Sudden death attributed to tracheobronchitis in absence of other reason
Case 9 76 WF	Bayliss[9] 1952 (Autopsy)	Serpentine, dilated branch of LADCA received small branch of RCA → PA. AV orifice = 1 cm. Heart dil. and hypert. Heart weight = 430 Gm.	160/70	Machinery	No evidence of functional disability except term. CHF. Pt. steadfastly denied ever having had dyspnea and orthopnea	Death from terminal heart failure and metastatic carcinoma of breast. Lesion believed due to anom. origin of an accessory coronary artery from the pulmonary artery
Case 10 85 WM	Colbeck[10] 1954 (Autopsy)	Fusiform aneurysm of RCA through a diffusely dil. serpentine vessel → RA via 4 small orifices. Card. hyper.; marked pulmonary edema. Heart weight = 554 Gm.	170/80	Systolic	Heart failure with dyspnea and edema for 18 months before death	Marked enlargement of LV on x-ray. Death from acute pulmonary edema
Case 11 58 WF	Davison[11] 1955 (Autopsy)	LCA → coronary sinus. Cardiac hypertrophy. Heart weight = 490 Gm.	125/55	Machinery	Heart failure—ascribed directly to shunt	Death due to lesion. Cardiac cath.: PA pressure = 75/25mm. Hg. Shunt = 3.9 L./min.; 55% of LV output
Case 12 55 WM	Knoblich[12] 1956 (Autopsy)	"AV fistula of the heart" with serpentine dil. LCA entering aneurys. sac and thereafter → vein leading to dil. myocard. capillaries. Heart weight = 600 Gm.	220/110	"Diastolic"	Heart failure and symptoms of hypertension	Exact route of AV shunt not clear from findings. Presence of significant shunt-flow evidenced by dilated vessels. Death from subarachnoid hemorrhage
Case 13 25 NF	Valdivia[13] 1957 (Autopsy)	Huge arteriovenous aneurysm RCA which → RA. Heart weight = 1800 Gm. (including aneurysm).	120/70	"Double"	Chronic heart failure with palpitation, fatigue and dyspnea	Neither angiocardiography nor exploratory thoracotomy allowed a correct diagnosis during life. Symptoms and death due to arteriovenous fistula
Case 14 * 15 WM	Biorck[14] 1947 (Surgery)	Probable anomalous dilated branch of LCA → PA. Anomalous branch ligated with disap. of thrill	135/80	Continuous	Decreased exercise tolerance	Surgery done for suspected PDA. Ligation of feeder artery resulted in disappearance of murmur. No recent follow-up

* In living patients, age given at time diagnosis was established.

TABLE 1.—*Case Summaries—Continued*

Age, ace, sex	Reference, author, year (Diagnosis by)	Pathologic data	Clinical data			Remarks
			Blood pressure	Murmurs	Reported symptoms of cardiac disease	
Case 15 * 9 WM	Paul[15] 1949 (Surgery)	Dilated, tortuous RCA → coronary vein at its junction with coronary sinus. No attempted ligation	110/75	Continuous	No	Pre-op. diagnosis of arteriovenous fistula; exact location in doubt but coronaries consid. Ligation not attempted. Pt. was asymptomatic (and still had murmur) at age 16
Case 16 * 16 WM	Gross[17] 1949 (cited by Paul) (Surgery)	Cirsoid, bulging nest of vessels in wall of LV. Probable drainage into low pressure structure on basis of thrill. No attempted ligation	Not stated	Continuous	Not clear. "Know heart disease since infancy." Had diagnosis of PDA and SBE made pre-op.	Operation for suspected PDA. Had been treated for SBE 6 weeks before operation. Not ligated. Apparently living at age 24
Case 17 * 11 WM	Sondergaard[19] 1955 (Surgery)	LCA → RV. Also PDA. Both ligated with disappearance of murmurs	Not stated	Continuous double	Dyspnea on exertion	Ligation followed by disappearance of signs and symptoms and dimunition in heart size. Cardiac cath. normal three months post-op. No recent follow-up
Case 18 * 19 NF	Davis[21] 1956 (Surg. & Cath.)	LCA → infundibulum of RV. Ligated with disappearance of thrill	110/80	Continuous	No	Surgery for suspected PDA. Ligation resulted in apparent cure. Pre-op. cardiac. cath. showed shunt volume of 1.7 L./min., 26% of LV output
Case 19 * 10 WM	Mozen[22] 1956 (Surgery)	Tortuous, cirsoid dilatation of LADCA which → LA (probably). Ligation with disappearance of murmur	130/60	Continuous also systolic	"Slight dyspnea on extreme exertion"	Normal cardiac catheterization. Diagnosis made at surgery. Ligation resulted in apparent cure
Case 20 * 8 WF	Walther[23] 1957 (Catheter)	Coronary artery → middle cardiac vein	130/84	Continuous	No	Cardiac catheterization: Fully saturated blood from middle cardiac vein. Shunted blood amounted to 47% of LV output
Case 21 * 14 WF	Walther[23] 1957 (Surgery)	RCA → PA or pulmonary conus. Ligation not attempted	120/70	Continuous	No	Surgery for suspected PDA. Ligation not attempted. Post-op. Cardiac Cath.: PA pressure = 33/17 mm. Hg. Shunt volume = 2.0 L./min., 29% of LV output
Case 22 * 6 WF	Present case (Angiocardiography)	Coronary arteriovenous fistula	106/72	Continuous	No	No evidence of disability during 7 years of medical observation

*In living patients, age given at time diagnosis was established.

Case 6. Emminger[6] described an arteriovenous fistula consisting of a serpentine, diffusely dilated right coronary artery that communicated with the great cardiac vein in a 43-year-old woman. The fistula was thought not to have caused cardiac disability; death was due to uremia complicating glomerulonephritis. Her blood pressure had been 150/65 mm. Hg. Detailed clinical data were not reported. In addition to the fistula, autopsy revealed that the markedly dilated coronary sinus opened into the right atrium through 2 fairly small ostia.

Case 7. Scott[7] in 1948 reported the case of an 84-year-old man without cardiac symptoms who died following prostatectomy. The patient's chest x-ray had revealed a right atrial aneurysm. At autopsy, there were found to be 17 aneurysmal dilatations involving 2 vessels, an accessory right coronary artery and a branch of the left anterior descending coronary artery. The largest aneurysm measured 10 by 8 by 8 cm. and was almost or completely clotted. A murmur had not been heard, and it is believed possible that the occlusion by laminated thrombus was responsible for this. The 2 aneurysm-bearing coronary arterial branches joined together and thereafter, through a common vessel, affected a small (1 mm.) communication with the pulmonary artery. As usual, the non-shunt-bearing coronary arteries were normal. The heart weighed 780 Gm.

Case 8. Brown and Burnett[8] described the case of a 13-month-old boy whose symptoms suggested patent ductus arteriosus, and who died of a purulent tracheal bronchitis. Physical findings included the demonstration of a pronounced thrill along the left sternal border. In addition, a continuous, machinery-like murmur was loudest in the third and fourth left interspaces. Both thrill and murmur seemed close to the surface. Blood pressure was 96/65 mm. Hg. Autopsy revealed the pressure of an abnormal communicating vessel arising adjacent to the normal left coronary artery and passing into a small recess in the right ventricle. The authors regarded it as a large left coronary artery "which had anastomosed early in development with intertrabecular spaces in the myocardium and thus established communication with the chamber of the right ventricle." The right ventricle was stated to be hypertrophied and moderately dilated. Neither the weight of the heart nor the appearance of the left ventricle was included in the description of pathologic findings.

Case 9. Bayliss and Campbell's case[9] consisted of a diffusely dilated communication between coronary and pulmonary arteries in a 76-year-old woman who was said to have been in good health until 2 years prior to death of terminal heart failure associated with carcinoma of the breast. She had had a loud, continuous murmur for at least 30 years. Blood pressure was 160/70 mm. Hg. Autopsy revealed that a large, tortuous, saccular aneurysm arose from the left anterior descending coronary artery and communicated with the right anterior sinus of Valsalva of the pulmonary artery. The heart weighed 430 Gm.; there was moderate enlargement and hypertrophy of both ventricles.

Case 10. Colbeck and Shaw[10] reported a coronary arteriovenous fistula in an 85-year-old man whose death in acute pulmonary edema occurred in a setting of heart failure of at least 18 months' duration. A harsh, grade IV systolic murmur without a thrill was present and the blood pressure was 170/80 mm. Hg. The electrocardiogram showed atrial fibrillation and left bundle-branch block. At autopsy, the heart weighed 554 Gm. and left ventricular hypertrophy and dilatation were present. There was also moderate enlargement and hypertrophy of the right atrium and ventricle. The lesion consisted of a large, fusiform aneurysm of the right coronary artery with connection to the right atrium by means of a serpentine anomalous communicating vessel.

Case 11. Davison et al.[11] reported a case wherein autopsy disclosed an arteriovenous fistula consisting of a diffuse, cirsoid dilatation of the circumflex branch of the left coronary artery which, after a serpentine course, entered an aneurysmally dilated coronary sinus. The patient, a 58-year-old woman, had noted palpitations for 10 years before death. Although at first clinical and electrocardiographic studies were normal, she subsequently developed a systolic murmur, increasing exertional dyspnea, orthopnea, fatigue, and the onset of atrial fibrillation. Ten months before death, a systolic and diastolic machinery-type murmur was heard over the pulmonary area. A systolic thrill was present. Blood pressure was 125/55 mm. Hg. Cardiac catheterization disclosed the pulmonary arterial pressure to be 75/25 mm. Hg and indicated the presence of a major left-to-right shunt at the atrial level. The total cardiac output was determined and equaled 7.1 L. per minute; while the shunt volume was 3.9 L. per minute (55 per cent of the total cardiac output). Death was ascribed to congestive heart failure. At autopsy, the heart weighed 490 Gm.; all its chambers showed dilatation and hypertrophy.

Case 12. Knoblich and Rawson[12] reported the autopsy finding of a long, tortuous, dilated, sclerotic, descending branch of the left coronary artery that communicated with a saccular coronary vein located in the ventricular septum. The patient, a 55-year-old man, had had systemic hypertension for years with blood pressures as high as 220/110 mm. Hg. Death was due to rupture of a congenital aneurysm of the basilar artery. A cardiac murmur had been present for at least 37 years; hypertension and cardiac enlargement had been known to

xist for at least 10 years. A harsh, grade III, iastolic apical murmur was heard repeatedly. Elec-ocardiographic findings suggested acute posterior-all infarction with extension into the septum. At utopsy, a coronary arteriovenous fistula located 1 the interventricular septum was encountered. his was presumed to have caused the electrocardio-raphic changes. The heart weighed 600 Gm., the ft ventricular wall measured 17 to 22 mm. in hickness, that of the right 5 mm.

Case 13. Valdivia et al.[13] recently described the utopsy finding of a large, presumably congenital neurysm of the terminal end of the right coronary rtery communicating with the right atrium. Their patient, a 25-year-old woman, had been known to have a cardiac murmur since childhood. X-ray studies 4 years prior to death demonstrated marked enlargement of the heart shadow. Angiocardiography done at that time did not result in satisfactory opacification. An exploratory operation established the presence of a large vascular tumor or aneurysm that could not be removed. Death occurred 4 years later due to heart failure. The diagnosis had not been established during life, despite angiocardiography and exploratory thoracotomy. At autopsy, a huge arteriovenous aneurysm was discovered. Its external measurements were 17 by 23 by 14 cm. The heart and aneurysmal mass together weighed 1,800 Gm. The aneurysmal cavity emptied into the right atrium through a 2-mm. opening.

In summary, of thirteen autopsied cases of coronary arteriovenous fistula collected from the literature, the structures in communication with coronary arteries were: coronary sinus, 4 cases (cases 2, 3, 5, and 11); coronary veins, 3 cases (cases 4, 6, and 12); pulmonary artery, 2 cases (cases 1 and 7); right atrium, 2 cases (cases 10 and 13); and right ventricle, 1 case (case 8).

Coronary Arteriovenous Malformations Established During Life

In 8 previously reported instances, explor-atory thoracotomy (7 cases) or cardiac catheterization (1 case) has established with reasonable certainty the diagnosis of coronary arteriovenous fistula. In 4 of these 8 patients, ligation of the communicating vessel was accomplished with apparent success.

Case 14. Biörk and Crafoord[14] in 1947 reported the finding at surgery of a communication between an aberrant branch of the left coronary artery and the main pulmonary artery. Their patient, a 15-year-old boy, had had decreased exercise tolerance for several years and exertional dyspnea since age 14. At age 7, a presystolic murmur was noted over the pulmonary area. It later became accentuated, exhibited systolic and diastolic components, and finally developed into a continuous murmur. The preoperative blood pressure was 135/80 mm. Hg. Radiologic examination demonstrated a rounded left heart border, prominent pulmonary artery segment, and hilar dance. The electrocardiogram was normal. Although the murmur was not regarded as characteristic, it suggested patent ductus arteriosus. At surgery, a thickened, abnormal vessel, probably arising from the left coronary artery, was seen to enter a pea-sized aneurysm-like sac on the pulmonary artery. That the continuous murmur was caused by this vessel was established by its ligation and the subsequent recovery of the patient. Four months later at follow-up examination, there was recorded a moderately harsh systolic but no diastolic murmur.

Case 15. Paul et al.[15] described a coronary arteriovenous communication that was discovered at surgery for a suspected patent ductus arteriosus. In their patient, a 9-year-old boy, blood traversed a diffusely dilated right coronary artery, a large venous plexus, and a coronary vein en route to the coronary sinus. No murmur had been heard at birth, but at the age of 2, in association with a transient hemiplegia of unknown etiology, a loud systolic murmur was first noted. Following scarlet fever at age 5, a loud apical systolic murmur, followed by a third heart sound and diastolic rumble, was described. Subsequently, the diastolic rumble disappeared, while there was a loud, continuous murmur along the lower right sternal border with maximum intensity occurring during systole. Blood pressure was 110/75 mm. Hg. The preoperative differential diagnosis was arteriovenous fistula involving the chest wall, the lung, or the coronary vessels. At operation, the coronary arteriovenous fistula was encountered, but its ligation was not attempted for fear of jeopardizing the myocardial blood supply. The patient continues to be well and is free of symptoms at 23 years of age.[16]

Case 16. Gross,[17] at thoracotomy for suspected patent ductus arteriosus, encountered a probable arteriovenous fistula of the coronary circulation in a 16-year-old boy. Heart murmurs had been present since birth and, preoperatively, a harsh, continuous murmur and thrill were maximum over the third and fourth left intercostal spaces adjacent to the sternum. Six weeks before surgery, the diagnosis of streptococcal endocarditis complicating patent ductus arteriosus had been made and a course of penicillin was given with apparent good results. At surgery, complete identification of the components of the fistulous communication was not possible, although a nest of bulging, thin-walled, vascular structures about 3.5 cm. in diameter and associated with a thrill was encountered

in the lateral wall of the left ventricle, slightly below the tip of the left atrial appendage. Ligation was not attempted. Gross states that the patient is currently performing hard manual labor without difficulty.[18]

Case 17. Sondergaard[19] ligated an aneurysmal connection between the left coronary artery and the right ventricle of an underdeveloped 11-year-old boy. Exertional dyspnea had been present since age 5, at which time a murmur had been noted. Preoperative physical examination revealed a continuous murmur (with thrill) possessing 2 areas of maximal intensity, one in the second and the other in the fourth left interspace. The second pulmonary sound was accentuated. At operation, a patent ductus arteriosus and an aneurysmal fistula were encountered. Both were ligated with the disappearance of all murmurs. Recent information discloses that the patient is now in excellent health.[20]

Case 18. Davis et al.[21] reported ligation of an anomalous left coronary artery communicating with the right ventricle in a 19-year-old Negro girl. Although the patient described no cardiac symptoms, a continuous machinery-like murmur was encountered, maximal in the pulmonary area. The electrocardiogram was normal, and there was no radiologic evidence of cardiac enlargement. Blood pressure was 110/80 mm. Hg. Catheterization of the heart disclosed normal right heart pressures, but indicated the entrance of highly oxygenated blood at the level of the outflow tract of the right ventricle. At operation, there was found to be diffuse dilatation of the left coronary artery, a branch of which entered the infundibular area of the right ventricle. Since temporary occlusion of this vessel resulted in disappearance of the thrill, ligation and division were accomplished. A small segment of the vessel was removed for histologic examination and found to be normal. Sixteen months postoperatively, the murmur had not reappeared. Although the electrocardiogram remained normal, postoperative x-ray films suggested slight cardiac enlargement (possibly due to pericardial reaction).

Case 19. Mozen[22] reported the ligation of a fistulous vessel connecting a cirsoid, aneurysmal dilatation of the anterior descending branch of the left coronary artery and the left atrium. The patient, a 10-year-old boy, had had a heart murmur since infancy, although his growth and development had been normal. Preoperatively, a soft systolic thrill was felt over the apex of the heart, and there was a loud continuous to-and-fro murmur with maximum intensity in the pulmonary area. A lower-pitched systolic murmur was also audible at the apex. Blood pressures ranged between 120/80 and 130/60 mm. Hg. Electrocardiographic and radiologic studies as well as cardiac catheterization revealed no abnormality. At operation, the cirsoid aneurysmal dilatation of the left descending coronary artery was found to be about 5 to 6 cm. in length and 0.5 to 1.3 cm. in diameter. Many large branches terminated in the left ventricular myocardium. One branch 1.5 cm. long and 0.5 cm. in diameter apparently emptied into the left atrium; ligation of this branch resulted in complete obliteration of the harsh thrill that it caused. It was stated, "this was a fistula which was carrying large amounts of blood from the high pressure aneurysm into the low pressure left atrium." In their report, published a year after surgery, the author stated that "heart sounds have remained normal."

Case 20. Walther et al.[23] reported the findings in 2 patients where the diagnosis of coronary arteriovenous malformation had been established during life. The first patient was an asymptomatic 8-year-old white girl who had developed normally in every respect and in whom a heart murmur had been heard during infancy. Her blood pressure was 130/84 mm. Hg, and the principal abnormality consisted of a grade V, roaring, continuous murmur (with thrill) maximal in the fourth and fifth left intercostal spaces close to the sternum. Electrocardiogram was unremarkable; slight left atrial enlargement was observed radiologically. At cardiac catheterization, the coronary venous system was entered and fully saturated blood withdrawn from the middle cardiac vein. The shunt-volume was calculated to be 5.2 L. per minute as compared to a cardiac output of 5.9 L. Pulmonary arterial pressure was 30/13 mm. Hg, and the right ventricular pressure was 30/6 mm. Hg.

Case 21. A second patient[23] reported by Walther et al. was a 14-year-old girl, who was known to have had a heart murmur since infancy, developed normally, and was asymptomatic. Blood pressure was 120/70 mm. Hg. A continuous machinery-type murmur was audible at the left sternal border, maximal in the second interspace. Radiographs were said to reveal slight increase in the transverse diameter of the heart (the published reproduction speaks for a left ventricular enlargement). The electrocardiogram was normal. Thoracotomy for a suspected patent ductus arteriosus failed to confirm the diagnosis. Instead, a thrill was palpated over the moderately enlarged pulmonary artery. The cause of this thrill was traced to an aneurysmally dilated right coronary artery that entered the right ventricular myocardium just proximal to the pulmonary valve. Since the thrill could not be completely abolished by compression of the dilated right coronary artery, ligation was not done. It was concluded that there was a communication between the right coronary artery and the outflow tract of the right ventricle or pulmonary artery. Cardiac catheterization subsequently revealed a high pulmonary

rtery oxygen content. Calculated shunt volume as 2 L. per minute, and was an impressive 28 er cent of the total cardiac output.

Discussion

Pathologic and Physiologic Considerations

Coronary arteriovenous communications re rare. The present series of 22 collected ases, probably the largest to date, indicates hat in comparison to coronary arteriovenous stulas primary tumors of the heart are elatively commonplace lesions since they are eported over 10 times as frequently!

It seems reasonable to postulate that congenital coronary arteriovenous fistulas may result from either or both of 2 forms of embryologic maldevelopment. The first consists of an embryonic arrest in the normal differentiation of the coronary vasculature. Probably the most primitive example of this type of developmental defect is the persistence of embryonal vascular sinusoids in the myocardium. Grant[30, 31] drew attention to the transient presence of blood-filled intertrabecular spaces within the myocardium of the normally developing mammalian heart. These spaces communicate freely with each other, also with the ventricular cavities and with the developing coronary vasculature. Postulating that arrest or faulty differentiation of the normal intertrabecular spaces gives rise to coronary vascular malfo mations, Wilson and Grant[32, 33] cited an example of multiform anomalies of the coronary and cardiovascular systems in a 14-month-old patient wherein blood-filled myocardial spaces communicated with coronary vessels. Burchell[34] in 1939 described large endothelium-lined sinuses within the wall of the left entricle of an adult dog stating that the inuses appeared to have functioned as arterovenous fistulas. Such sinusoids have been bserved repeatedly in human autopsy maerial,[33, 35-39] usually in association with nomalous origin of the left coronary artery rom the pulmonary artery. In certain intances a significant arteriovenous shunt vidently occurred; in others, it apparently id not. The vascular resistance of such lesions determines the extent of abnormal shunting. Because of the difficulty in assessing shunt-function in reported cases of persistent myocardial sinusoids, these lesions have not been included in the present review of coronary arteriovenous communication.

Certain congenital arteriovenous fistulas are believed to reflect a developmental defect occurring at a later stage in the fetal maturation of the coronary system than that resulting in the persistence of primitive myocardial sinusoids. In support of this, is the fact that while the gross lesion of the usual fistula may appear quite complex, many of the changes are secondary to the shunt. Unlike the undifferentiated sinusoids, the vessels of the more mature lesion bear a reasonable resemblance to arteries and veins. To extend this reasoning, the coronary arteriovenous malformation could be regarded as a more mature lesion than the usual peripheral arteriovenous fistula where innumerable functioning or potentially open sites of transcapillary communication exist. This fortunate difference is probably essential to successful surgery in coronary arteriovenous lesions for if, as in peripheral lesions, new openings were to develop following the ligation of evident sites of communication, death might well be hastened rather than postponed.

The second major mechanism responsible for the formation of coronary artery fistulas involves the anomalous origin of a coronary artery. As was exemplified by Abbott's case[1] and by other cases not included in this review,[40-43] intercoronary anastomoses may allow a reversal in the direction of flow through the anomalous coronary artery. If the coronary resistance at the anastomotic site is sufficiently low, the pressure gradient is such as to favor flow from the normally originating coronary artery through the anomalous branch into the pulmonary artery or the right ventricle.

Despite the frequency with which the term arteriovenous aneurysm is used, confusion appears to exist concerning the relationship between coronary arteriovenous communications and coronary artery aneurysms.

Authors have reviewed the findings in collected cases of coronary aneurysm without mentioning or stressing the important etiologic role of arteriovenous communications.[24-29] That the association is important is evidenced by analogous extracoronary arteriovenous shunts. Given a sufficient shunt volume acting over a long enough period, there must result dilatation of the shunt-bearing structures. This is true of the vessels involved in peripheral arteriovenous shunts of any cause;[44] it is true of the structures carrying recirculated blood in patients with interatrial septal defects; and it is also true of coronary arteriovenous communications. In several published cases of "arteriosclerotic" or "mycotic-embolic" coronary aneurysms, diffuse dilatation (usually termed a cirsoid or serpentine aneurysm) points directly to a probably undetected but causative fistulous lesion. Particularly convincing in this respect are cases where the dilatation involves a coronary artery down to and including one of its branches but spares other branches and the vessel itself beyond the point where the dilated shunt-bearing branch is given off. Since the relationship was apparently overlooked, previously reported cases cannot serve as basis for quantitating the etiologic relationship. The frequency with which current reports have dealt with aneurysmal dilatation secondary to arteriovenous communications rather than with coronary artery aneurysms offers evidence of the increasing awareness of this previously unrecognized causative relationship. The study of known instances of shunt-caused aneurysms explains why the primary communication escaped autopsy detection in others. In case 7, for example, 17 aneurysms existed, the largest measuring 10 cm. in maximum diameter, while the orifice of communication was but 2 mm. wide. Similarly, case 13 exhibited an aneurysm measuring 23 cm. in diameter, but a communicating orifice of only 2 mm. An argument that such large aneurysms could not result from such tiny communications is not valid; the contrary, of course, is the case. It is difficult to explain a genuine continuous murmur on the basis of simple aneurysmal dilatation. It would be illogical to assume that arteriosclerosis is the cause of the majority of coronary aneurysms, since, as has been emphasized by Scott,[7] while coronary aneurysm is rarely seen, coronary arteriosclerosis is, comparatively speaking, neither rare nor as likely to give rise to large dilatations. Furthermore, the fact that atherosclerosis is present in a coronary artery aneurysm is not surprising, since secondary atheromatous changes occur in a wide variety of aneurysms.

The pathophysiology of coronary fistulous communications is essentially that of arteriovenous fistulas elsewhere in the body with the exception that the former may result in myocardial ischemia in addition to the usual increase in cardiac output. Regardless of the site, in any functional fistulous communication, blood flows from a high pressure system to a low pressure system. If there were no pressure gradient, there would be no flow. As a consequence of the increased volume of flow there occurs dilatation of the affected coronary arteries and the vessels or chambers receiving the shunted blood. The clinical consequences are almost entirely determined by the shunt-volume and its duration. The shunt-volume is, in turn, dependent upon coronary vascular resistance. Thus, when persistent embryonal sinusoids are the sole lesion present, physiologic consequences would tend to be slight due to a fairly high coronary resistance.

Given sufficient shunt-volume acting over a long enough period of time, left ventricular hypertrophy and failure must inevitably occur. In coronary, as in other systemic arteriovenous communications, there may occur an increase in blood volume, heart rate, and pulse pressure, as well as other evidences of high-output failure.[44]

Clinical Features

Age, Sex, and Race. The ages of the 22 patients comprising this series ranged from 13 months to 85 years. In view of the small

series and wide age range, the figure for average age would be more misleading than useful. The 8 living patients were relatively young compared to the autopsied patients. It is not surprising that the published case reports of the living patients are of relatively recent vintage in view of the heightened interest and diagnostic abilities resulting from the recent emergence of surgery as a definitive method of treatment for many congenital cardiovascular lesions. Of the entire group of cases, 12 were male, 10 female. Three patients were Negroes.

Symptoms and Signs. Cardiovascular symptoms occurred in 11 of the 22 patients, but the lesion was apparently regarded as responsible for symptoms in only 6 of these; 2 autopsied cases (cases 11 and 13) and 4 surgically proved cases (cases 14, 16, 17, and 19). In 3 or 4 cases, the statement that symptoms had not existed apparently was based upon hearsay rather than clinical observation. The autopsy findings cast doubt upon the contention that coronary arteriovenous fistula is usually a benign lesion. Findings such as those in case 13 leave little doubt as to the potentially serious nature of the anomaly. Cardiac symptoms are those of heart failure due to the increased cardiac output occasioned by a left-to-right shunt. Five cases exhibited clear-cut evidence of chronic heart failure; and among the reported symptoms and signs of this were dyspnea, peripheral edema, pulmonary congestion, and fatigue.

Laboratory Data. Electrocardiographic studies in our case and in the other 7 patients diagnosed during life were not remarkable. The electrocardiograms of the autopsied patients were frequently abnormal. Case 7 had premature atrial beats and a shifting pacemaker. Case 9 exhibited left axis deviation and left ventricular predominance (moderate hypertension may have been a contributory factor). Case 11 had a normal electrocardiogram 5 years prior to death but exhibited terminal atrial fibrillation and right axis deviation without ventricular predominance. Case 10 showed atrial fibrillation and left bundle-branch block. In case 12, there existed for at least 3 years, an unchanging elevation of the S-T segments suggestive of septal injury. The patient had had severe hypertension for several years. At autopsy a coronary artery aneurysm, located in the septum, was discovered and believed to be responsible for the electrocardiographic changes. The authors, Knoblich and Rawson,[12] suggested that the fixed electrocardiographic abnormality favored some lesion other than myocardial infarction. Generally speaking, the data from the 22 patients comprising this series suggest that electrocardiographic changes, when they exist, are not very helpful in establishing the diagnosis of coronary arteriovenous communications.

Cardiac catheterization was performed in 5 of the patients of this series. In case 19, shunted blood apparently entered the left atrium and shunt volumes could therefore not be calculated (other findings at catheterization were normal in this patient). In the 4 others, cases 11, 18, 20, and 21, hemodynamic data are available and have been summarized by Walther et al.[23] The observed shunts ranged from 1.7 L. per minute to a maximum of 5.2 L. per minute. In this lesion, the pulmonary flow is equal to the left ventricular output, and the latter represents the sum of the peripheral flow plus the shunt flow. Expressed as percentages of left ventricular output, the shunts were as follows: case 11, 55 per cent; case 18, 26 per cent; case 20, 47 per cent; case 21, 29 per cent. The mean shunt volume of all 4 patients was 39 per cent. Stated differently, about 40 per cent of the work of the heart was wasted. Pressures in the pulmonary artery of case 11 were 75/25 mm. Hg, indicating the development of pulmonary vascular disease. Case 18 revealed normal right heart pressures, while cases 20 and 21 showed slight pulmonary hypertension (probably this was significant since both were children). It is evident that the determination of blood oxygen content in various regions may be highly significant in establishing the diagnosis

of coronary arteriovenous shunting of the blood, particularly where the communication occurs via a coronary vein that is successfully catheterized. Lacking this, the findings could mimic more common cardiac anomalies such as interatrial and interventricular septal defects, patent ductus arteriosus, or aorticopulmonary septal defects. Similar blood oxygen findings could result from rupture of an aortic sinus into one of the right heart structures.

X-ray examination by conventional technics is of value insofar as there are present grossly recognizable changes in the cardiovascular silhouette. The demonstration of an aneurysmal dilatation, when it exists, might be of aid in distinguishing coronary arteriovenous fistulas from high interventricular septal defects or patent ductus arteriosus. Radiologic appraisal of heart size offers a useful means of gaging the functional significance of the lesion. In 7 of the autopsied cases, roentgenograms were available; 5 were described and said to reveal cardiac enlargement. Colbeck and Shaw[10] identified intracardiac calcification that at autopsy was found to lie within the coronary artery aneurysm (case 10). In case 13, the chest film showed marked enlargement of the cardiac silhouette due to the massive aneurysm that was present. In Scott's patient (case 7), a large globular mass causing esophageal displacement was demonstrated adjacent to the right heart border. Of the 8 living patients, Biörck and Crafoord's[14] patient (case 14) revealed rounding of the left heart border as well as enlargement and increased pulsation of the pulmonary artery and hilar branches. The findings reverted to normal following successful surgical interruption of the fistula. Both of Walther's[23] patients (cases 20 and 21) were reported to have shown slight enlargement of the heart and prominence of pulmonary arteries on radiographic examination. In the remaining 5 cases, including our own, the heart was normal in size and contour and abnormalities of the pulmonary artery or pulmonary vasculature were not recognized. Following surgery, in case 18, there was slight enlargement of the heart 16 months after operation, a finding possibly attributable to postoperative pericardial changes.

Special contrast visualization offers much in the diagnosis of coronary arteriovenous fistulas. Angiocardiography can be expected to reveal moderate- to large-sized coronary artery aneurysms providing technically adequate studies are made. Neither angiocardiography nor thoracotomy resulted in a correct antemortem diagnosis in case 13; the former because of marked cardiac dilatation and consequent excessive dilution of the contrast agent, the latter because the anatomy of the lesion was such as to discourage manipulation for diagnostic or therapeutic reasons. Angiocardiography was performed in our patient and made the correct diagnosis possible. Cirsoidal dilatation of the feeding coronary artery was clearly visualized, although the site of the fistula was not determined. The study suffered from patient movement during the examination, a factor that now can be eliminated by the use of millisecond exposure technics.[45] It is obviously desirable to employ studies in 2 projections (or stereoscopic sequencing) and rapid serial-recording technics.

Coronary arteriography by the controlled approach of occlusion aortography,[46] stands to offer the most precise anatomic diagnosis of coronary arteriovenous fistula that can be achieved during life, and should prove superior to surgical exploration in this respect. To date, there has been no opportunity to demonstrate this conviction. Angiocardiography offers a more useful method for study of the heart and great blood vessels as a whole, but is distinctly inferior in the ability to produce satisfactory coronary visualization. Selective technics such as aortography, while providing optimum opacification of particular regions, suffer from their inability to reveal structures that in terms of blood flow are proximal to the site of injection. Inasmuch as angiocardiography is simpler to perform, bears a somewhat lower risk than aortography, and reveals a

greater total amount of information about the heart as a whole, it is recommended as the initial procedure of choice if there is any doubt about the exact nature of the lesion in question. In coronary arteriovenous communications, angiocardiography during opacification of the right heart structures should demonstrate a filling or mixing defect at the site of shunts as large as those in the 4 cases studied by cardiac catheterization. It should be emphasized that any compromise in technical quality, particularly the use of detail-destroying slow exposures will seriously limit the approaches just discussed.

Diagnosis. The diagnosis of a coronary arteriovenous fistula depends upon the evaluation of a continuous precordial murmur especially when its location is unusual. Most continuous, machinery-like murmurs are best heard at the pulmonary area and reflect the presence of a patent ductus arteriosus. A somewhat lower location of the site of maximal intensity might indicate an aortico-pulmonary septal defect or a ruptured aortic sinus aneurysm, 2 other lesions capable of causing similar murmurs. In the latter, the abrupt onset of the murmur in association with chest pain, provides a valuable clinical lead to the diagnosis. Unlike coronary arteriovenous fistulas, pulmonary arteriovenous fistulas often are associated with other vascular anomalies and exhibit a strong tendency to occur in families. When a murmur is present, it is also located over the lung fields. Pulmonary arteriovenous fistulas are usually identifiable by conventional chest roentgenography and are obvious by angiocardiography.[47] Arteriovenous fistulas of the chest wall, muscles, and internal mammary vessels[48-50] also may enter into differential diagnoses.

On the basis of this collected series of cases, it appears that murmurs due to coronary arteriovenous fistulas may be heard at various locations depending upon the site of the fistulous communication. In our case, since the fistula was close to the apex of the heart, the resultant murmur was similarly located, appeared to take origin close to the stethoscope and was intensified during expiration.

If a continuous murmur is judged to represent something other than a patent ductus arteriosus (and location may be the most important means of making the distinction), additional studies such as cardiac catheterization, angiocardiography, and aortography provide means for making a nonsurgical diagnosis in the living patient.

Prognosis and Treatment. The prognosis in this lesion like other arteriovenous shunts depends upon the volume and duration of the shunt as well as the ability of the heart to handle the increased load.[44] The cases reviewed here demonstrate the wide range of functional disability that can result. Thus, the most useful generality referable to prognosis and therapy would be the suggestion that the findings exhibited by the patient are a better guide than any set policy, conservative or otherwise. It may be worthwhile to summarize the evidence bearing upon prognosis provided by this series.

By repeated use of "remarkably well tolerated"[12, 15] and other similarly optimistic comments, several previous authors have indicated their belief that coronary arteriovenous fistulas do not carry a poor prognosis. It should be noted, however, that with 1 exception,[23] personal observations have been limited to single cases. Furthermore, a critical review of published reports suggests that the optimism of some authors is unsupported by their data.

Knoblich and Rawson[12] reported the autopsy findings in an arteriovenous fistula of the heart that occurred in a 55-year-old business man who died of a subarachnoid hemorrhage. In ascribing the marked cardiac enlargement that was present (600 Gm.) to the patient's hypertension (220/110 mm. Hg), they made no mention of the frequent association of arteriovenous shunts and systemic hypertension. Noting marked serpentine dilatation of the left descending coronary artery and a saccular vein with which it communicated, the authors attributed this to "markedly reduced capillary

beds through which blood entering the terminal portion of the artery had to pass.'' This interpretation and the assumption that the patient's hypertension was independent of his arteriovenous fistula are both inconsistent with the observed hemodynamic behavior of arteriovenous fistulas including those in this series. Reduction in flow through vessels leads to the opposite of dilatation; the reverse occurs in arteriovenous fistulas. When they concluded that ''arteriovenous fistulas of the heart do not appreciably shorten the life span,'' Knoblich and Rawson appear to have disregarded the possibility that their patient who died in 1955 at the age of 55 years would, but for his illness, have enjoyed a life expectancy of 19.3 additional years.[51]

The age at death of some of the patients in this series might seem to support the contention that longevity is the rule in coronary arteriovenous fistula. This is simply not true. The mean age of death of 13 autopsied patients was 55 years, while the range was from 1 to 85 years. Four patients died without reaching their forty-fourth year of life. The average figure for life expectancy at the age at which the 13 autopsied patients in this series died is 21.6 years.* This figure could mislead the unwary, since it fails to take into account other causes of death. Inasmuch as it reflects actuarial factors such as the year in which death occurred and the age and sex of the patients, it is more meaningful than a figure expressing the average age at death. This short series demonstrates that longevity is possible with a coronary arteriovenous fistula, but provides little or no useful information about the life expectancy of patients with this lesion.

Convincing evidence exists to show that coronary arteriovenous malformations are indeed potentially serious lesions. Heart weights were stated in 9 of the 13 cases where autopsy was done. Without exception, the figures were above normal. Heart weights ranged from 380 to 1,800 Gm. with a mean of over 700 Gm.

In this series of 13 autopsied patients, death was directly attributed to the shunt only twice (cases 4 and 11). Although the authors did not discuss the cause, it is apparent that the death of case 13, a 25-year-old woman reported by Valdivia et al.[13] was a result of her fistulous communication. Review of the autopsied cases indicates that death probably resulted from congestive heart failure in 6 of the reported patients (cases 3, 4, 9, 10, 11, and 13). In a total of 12 of the 22 patients comprising this series, there were definite cardiovascular symptoms. Although myocardial infarction (case 3) and hypertension (cases 4, 10, and 12) may have been independent contributory factors, it is equally possible that both may have resulted from or added to the disability due to the fistulous communication. The tendency for gangrenous changes to occur in extremities affected by peripheral arteriovenous fistulas is well known and suggests that coronary arteriovenous communications may predispose to or aggravate myocardial ischemia and infarction. Similarly, it is apparent that when a sufficient shunt volume exists, there will necessarily be an increase in the systemic, systolic, and pulse pressures. For example, although the lethal heart failure in case 4 probably was due to hypertension (260/100 mm. Hg), it is also probable that the hypertension was due to or aggravated by the fistula. The pulse pressure of 160 mm. Hg offers support to this interpretation as do many reports of reversible but serious hypertension associated with peripheral arteriovenous lesions.

In 4 of the 22 cases comprising this series, cardiac catheterization allowed the calculation of the volume of shunted blood. This ranged from 2.0 to 3.9 L. per minute, with the average shunt of the 4 patients accounting for slightly more than 40 per cent of the average cardiac output. Although shunts of

*The figure of 21.6 years represents the calculated but obviously hypothetical number of years of life expectancy the average patient might have looked forward to had he been normal at the time of death.[51]

this magnitude may be well tolerated in many individuals, they necessarily represent a threat to the patient's well being and longevity.

Certain lesions would be difficult or impossible to correct by presently available surgical methods. On the other hand, in all of the 4 instances wherein an attempt was made to ligate the involved coronary artery or branch, the patients appear to have been cured, as evidenced by the disappearance of the continuous murmur in all cases, and symptoms in the 2 cases where they existed preoperatively. Ligation was not deemed advisable in 3 of the 7 patients subjected to thoracotomy on the basis of the anatomic conditions encountered. Furthermore, the 3 patients who were explored without ligation appear to have survived none the worse for the procedure. Thus, it appears that surgery may offer much to patients suffering with this lesion. The possibility of successful surgical management will be dependent upon the type of communication present in a given case. Where a single anomalous vessel is present, the surgeon should attempt to demonstrate that occlusion of this channel is safe and eliminates the thrill. Final closure should probably not be carried out until it is demonstrated that clinical or electrocardiographic evidence of impaired myocardial blood supply does not follow temporary occlusion of the shunt-bearing branch. In complex, cirsoid communications surgical obliteration of the anomalous channels might prove to be hazardous by virtue of technical difficulties and because the multiple ligations requisite for closure might produce regional myocardial ischemia. It is in such cases that the lesion is most apt to cause serious functional consequences, however, and again the decision must be based upon the evidence provided by the case in question.

In our case, because of the asymptomatic course and absence of cardiac enlargement, as well as the normal and unchanging electrocardiographic findings during 7 years of observation, surgical exploration has not to date been considered necessary. Insofar as there has been no evidence of progression of the disease, the time gained has already brought the patient into a new era of cardiac surgery—the surgery of the open heart. In this respect, her chances for cure have been materially improved. Since, as in other types of arteriovenous fistulas, bacterial endocarditis represents a potential complication, antibiotic prophylaxis is used for dental extractions and other minor surgical procedures. Medical observation will be continued with emphasis placed upon functional testing. Should there be evidence of progression of the disease, surgery will be seriously considered.

Summary

Twenty-one cases of coronary arteriovenous communications have been collected from the literature and a single case has been added. Coronary arteriovenous communications appear to result from 1 or a combination of 2 types of mechanisms causing defective fetal development.

Type 1. Defective Differentiation of Coronary Capillary Elements. Primitive sinusoidal elements of the coronary system may persist or undergo defective development resulting in communications between the coronary arteries and the coronary veins or the chambers of the heart. If such communications present a sufficiently low resistance to coronary blood flow, an arteriovenous shunt is the result.

Type 2. Anomalous Coronary Artery Origin with Intercoronary Communication. When, through defective formation of the primitive bulbar septum, a coronary artery takes its origin from the pulmonary artery or the right ventricle, intercoronary anastomoses sometimes permit blood to flow from the high pressure systemic coronary circuit into the low pressure pulmonary circuit. This mechanism, though a common cause of coronary arteriovenous fistulas, is a less frequent manifestation of anomalous coronary artery origin, since intercoronary vascular resistance usually prevents significant

shunting. It is apparent that defective capillary differentiation and anomalous coronary artery origin are often jointly responsible for coronary arteriovenous fistulas.

Perhaps as many as a third of previously reported coronary artery aneurysms have resulted from congenital coronary artery fistulas, a fact sometimes overlooked.

The diagnosis of coronary arteriovenous fistula can be made with certainty and precision during life. It may be suspected on the basis of a continuous murmur resembling that of patent ductus arteriosus but atypical in location. Catheterization of the heart may be diagnostic and can be expected to reveal the presence and volume of a left-to-right shunt. It also might prove to confuse the diagnosis by suggesting a more common cause of such a shunt. Angiocardiography is capable of diagnostic findings. Coronary arteriography, though yet to be used in coronary arteriovenous fistula, probably offers the best means of obtaining a precise anatomic diagnosis during life.*

The prognosis in this lesion varies widely in keeping with the varying anatomic and functional abnormalities that may exist. In some instances there has been long life with apparent freedom from symptoms; in others, heart failure due to the demand for increased cardiac output or associated hypertensive disease has caused death of patients with this lesion.

Surgical ligation of the artery or arteries carrying blood to the fistula should be attempted if there is evidence of progressive disease. In a given case, surgery may be curative or it may be impossible, depending upon the pathologic anatomy that is present.

ADDENDUM

R. M. Cooley and R. B. Sloan (*Radiology of the Heart and Great Blood Vessels,* Baltimore, Williams & Wilkins, 1956, p. 226, fig. 141) have also illustrated an asymptomatic child with a coronary arteriovenous fistula. Diagnosis was suspected after clinical studies and confirmed by angiocardiography.

*This has recently been achieved by Dr. B. A. Gasul and associates and briefly described by Dr. E. A. Fell.[58]

SUMMARIO IN INTERLINGUA

Vinti-un casos de communication inter arteria e vena coronari esseva colligite ab le litteratura. Un vinti-secunde caso es addite. Communicationes inter arteria e vena coronari pare resultar ab 1 o un combination de ambes de 2 typos de mechanismo effectuante un defective disveloppamento fetal.

Typo 1. Differentiation Defective del Elementos Capillari Coronari.—Primitive elementos sinusoide in le systema coronari pote persister o sequer un disveloppamento defective que resulta in communicationes inter le arterias coronari e le venas coronari o le cameras del corde. In casos in que tal communicationes presenta un sufficientemente basse resistentia al fluxo de sanguine coronari, le resultato es un derivation arterio-venose.

Typo 2. Origine Anormal del Arteria Coronari con Communication Intercoronari.—Quando, in consequentia del formation defective del primitive septo bulbar, un arteria coronari prende su origine ab le arteria pulmonar o ab le ventriculo dextere, anastomoses intercoronari permitte a vices un fluxo de sanguine ab le systemic circuito coronari con su alte pression verso le circuito pulmonar con su basse pression. Iste mechanismo es un causa commun de fistulas inter arteria e vena coronari, sed illo es minus frequentemente un manifestation del origine anormal del arteria coronari, proque le resistentia vascular intercoronari preveni usualmente grados significative de derivation. Il es apparente que le defective differentation capillari e le origine anormal del arteria coronari es frequentemente coresponsabile pro le formation de fistulas inter arteria e vena coronari.

Il pare que multes e possibilemente non minus que un tertio del previemente reportate aneurysmas de arteria coronari esseva le resultato de congenite fistulas de arteria coronari. Iste facto es non infrequentemente negligite.

Le diagnose de fistula inter arteria e vena coronari pote esser establite con certitude e con precision durante le vita del patiente. Illo pote esser suspicionate super le base de un murmure continue que resimila le mur-

mure de patente ducto arteriose sed differe ab isto in su location. Catheterisation del corde pote establir le diagnose. Il es a expectar que illo revela le presentia e le volumine de un derivation sinistro-dextere. Il es etiam possibile que catheterisation confunde le diagnose per suggerer un causa plus commun del derivation. Le angiocardiographia es capace a contribuer datos de valor diagnostic. Arteriographia coronari — ben que non ancora usate in casos de fistula inter arteria e vena coronari—representa probabilemente le melior methodo pro obtener un precise diagnose anatomic durante le vita del patiente.

Le prognose in casos de iste lesion varia extensemente, de accordo con le varie anormalitates anatomic e functional que pote esser presente. In certe casos, longe periodos de superviventia con apparente absentia de symptomas esseva notate. In alteres, insufficientia cardiac—causate per le requirimento de un augmentate rendimento cardiac o per le presentia associate de morbo hypertensive—ha causate le morbo de patientes con iste lesion.

Le ligation chirurgic del arteria o del arterias que porta sanguine verso le fistula debe esser essayate in casos de evidente morbo progressive. In le caso individual, intervention chirurgic pote esser curative o illo pote esser impossibile, in dependentia del anatomia pathologic que es presente.

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Blood Supply of the Human Interventricular Septum

By THOMAS N. JAMES, M.D., AND GEORGE E. BURCH, M.D.

The blood supply of the interventricular septum has been studied in 43 normal human hearts, from patients dying of noncardiac causes. The specimens were prepared by injection of vinylite into the coronary arteries. Description is made of the normal vascular anatomy of this area, and its clinical importance is discussed.

ALTHOUGH the interventricular septum comprises a large portion of the myocardium, study and description of its normal blood supply have been neglected; one standard textbook of anatomy fails even to mention it.[1] This lack of attention may be attributed to its relative inaccessibility for anatomic studies without disturbing its structural relationships. Injection of colored opaque solutions, followed by clearing in various oils, fails to display the interventricular septum adequately.[2, 3] Stereoscopic roentgenograms of injected coronary arteries result in overlapping of septal vessels to such an extent that their individual identification becomes difficult, if not impossible.[3] "Unrolling" the heart before the roentgenograms are taken[4] isolates the septum but also removes it from its spatial orientation.

Laubry, Soulié, and Thys[5] injected radiopaque material into the coronary arteries and then obtained roentgenograms of the isolated interventricular septum, whereas Hermanek[6] examined the blood supply of this region by dissection alone; both these studies, however, were concerned primarily with infarction and coronary anastomoses in the septum.

For examination of the normal blood supply of the heart a more satisfactory method is injection of a noncorroding substance into the arteries, followed by corrosion of the supporting structures to leave a cast of the arteries. Additional casts of the cardiac chambers result in a spatially oriented replica of the entire heart.[7] Casting of the chambers of only one side of the heart makes possible examination of the vessels in the interventricular septum. This method was employed in the present study to obtain information regarding the normal blood supply of the human interventricular septum.

MATERIAL AND METHODS

Forty-three human hearts, of patients (32 men and 11 women) who died of noncardiac causes, were examined. Ages ranged from 12 to 81 years, with similar frequency distribution in each decade except for the eighth and ninth decades of life, which contained 1 patient each.

These hearts were normal in weight and the ventricles on gross inspection were not hypertrophied. In all hearts the valves were examined under direct vision through the aorta, main pulmonary artery, venae cavae, and pulmonary veins; in this series none of the hearts had pathologic valves. The coronary arteries were inspected at their ostia prior to cannulation, and for their entire length where visible in the epicardium; the arteries of all hearts in the series were patent for their visible length and none exhibited atherosclerosis of a degree indicative of compromising blood flow. The hearts and other gross organs of these patients were normal in color (specifically no remarkable pallor), but antemortem hematologic data were not available. There were no gross lesions of the myocardial surface, such as fibrosis or infarction.

The arteries were injected with vinylite resin, and the tissue was subsequently removed with concentrated hydrochloric acid, according to a technic previously described.[7, 8] Although casts of either the right or left ventricles were made in various hearts, casts of the right chambers resulted in better retention of the normal shape of the heart.

RESULTS

The interventricular septum of man receives most of its blood supply from the left

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This work was aided by grants from the U. S. Public Health Service (H-143) and the Upjohn Company, Kalamazoo, Mich.

FIG. 1. Photograph of the right lateral aspect of the vessels in the interventricular septum. See figure 2 for anatomic orientation. Branches of the right coronary artery (the dark undulating trunk crossing the upper heart) have been cut off to reveal the septum. The lighter vessels on the right side of the photograph are the left anterior descending coronary artery and its septal branches. On the left side of the photograph may be seen the short septal branches of the posterior descending coronary artery, which are darker. The lighter vessel, which has a wrinkled appearance, at the extreme left margin is the posterior interventricular vein.

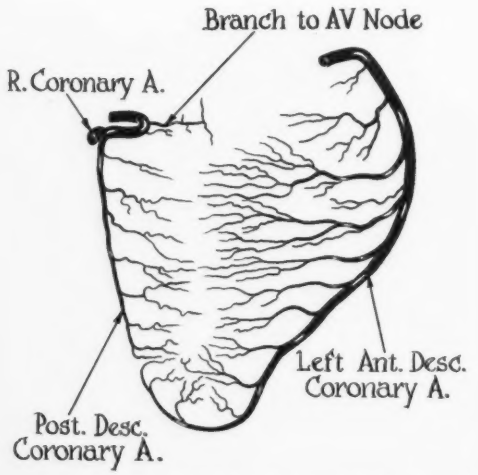

FIG. 2. Drawing of the blood supply of the normal human interventricular septum. Note the preponderance of supply by the left anterior descending coronary artery, and the U-turn of the posterior right coronary artery, which gives off the branch to the atrioventricular node.

anterior descending coronary artery (figs. 1 and 2). These septal arteries from the anterior interventricular sulcus were usually 40 to 80 mm. in length. They coursed diagonally in an anteroposterior direction, slightly caudally, describing a gentle curve with convexity to the right. The anterior descending artery was well developed in all hearts, and comprised the only branch of the left coronary artery in 2 hearts. It always reached the apex cordis and in most hearts coursed around onto the lower posterior interventricular sulcus, ascending for a distance of 10 to 50 mm.

The anterior penetrating septal arteries entered from the epicardium near the right ventricular side of the septum and remained near the right ventricular endocardium for the initial part of their septal course (fig. 3). These long penetrating arteries terminated in a relatively straight direction, as opposed to the right angle terminal branching of the arteries of the free wall of the left ventricle. The penetrating septal branches of the posterior descending coronary artery (the terminal right coronary artery in 41 of the 43 hearts) were relatively short, seldom being more than 15 mm. in length.

In the upper portion of the septum posteriorly, the right coronary artery made a unique U-turn deep to the posterior interventricular vein, to penetrate the junction of the interventricular and interatrial septa in the region of the atrioventricular node (figs. 2 and 4). At this point the right coronary artery gave off a relatively large branch from the apex of the U-turn, which continued for a distance of about 25 mm.

Gross anastomoses were found within the interventricular septum between the right and left coronary arteries. In the free walls of the ventricles adjacent to the septum anas-

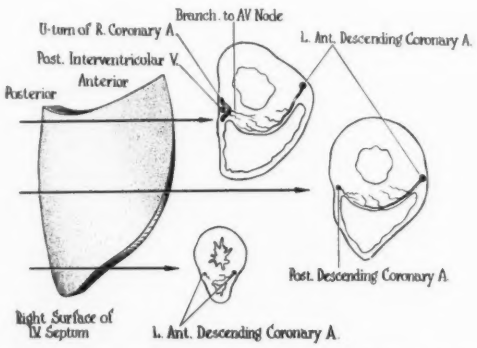

FIG. 3. Left, a planar diagram of the contour of the human interventricular septum as viewed from the right ventricular side. The long arrows point to cross-sections from the corresponding levels in the planar diagram. In the section from the upper septum are seen the longest septal branches of the posterior descending artery. From the mid-septum (the muscular portion) the cross-section illustrates the predominance of supply by the anterior penetrating arteries. The cross-section near the apex depicts both the anterior and posterior septal branches as derived from the left anterior descending artery, since this artery passes around the apex to the posterior wall. In all the cross-sections note the proximity of the septal branches to the right ventricular endocardium and the lack of perpendicular terminal branching which is characteristic of terminal arteries in other areas of thick myocardium.

tomoses could also be seen communicating with the main arterial trunks overlying the septum. The anastomoses most frequently found were located in the following sites:

1. Between the anterior and posterior penetrating septal arteries, particularly in the midportion of the septum.

2. Between the upper 2 cm. of the left anterior descending artery and the first 2 cm. of the right coronary artery by way of the ring of Vieussens (fig. 5), and between right ventricular branches of the left anterior descending artery and the straight branches of the right coronary artery.

3. Between the left anterior descending artery and the posterior descending artery around the apex cordis.

4. Between the posterior descending coronary artery and branches of the right marginal and left marginal arteries crossing horizontally over the posterior wall of the heart.

5. Between small arteries (in 2 hearts) behind the aorta, connecting the initial centimeter of the right coronary artery and the main left coronary artery.

One heart exhibited a large unusual branch of the right coronary artery in the first centimeter of its origin that turned in an opposite direction to the main right coronary artery, coursed behind the aorta caudally, turned anteriorly deep to the main left coronary artery, and reappeared in the midportion of the anterior interventricular sulcus. Throughout its course it distributed branches to the interventricular septum.

In addition to the penetrating branches from the anterior and posterior descending arteries, other branches from neighboring arteries in the free ventricular walls frequently coursed over to the anterior and posterior interventricular sulci, turned 90 degrees, and penetrated the septum for various distances. These branches were not large or numerous but may represent potential channels for collateral circulation. Such branches originated anteriorly from the left circumflex artery, the left straight arteries, and the left marginal artery; they originated on the posterior surface from both the right and left marginal arteries.

The variation in number, length, and courses of the anterior penetrating septal arteries was too wide to permit descriptive classification. In general the fewer the branches, the larger they were.

The origin of arteries to the interventricular septum was estimated to be in about the following proportions:

1. In 7 hearts, 60 to 70 per cent of the septal blood supply was provided by branches from the left anterior descending artery, and the remainder by branches from the posterior descending artery.

2. In 9 hearts, 70 to 80 per cent was provided from the anterior descending artery.

3. In 15 hearts, 80 to 90 per cent was provided by branches from the anterior descending artery.

4. In the remaining 12 hearts, 90 to 100

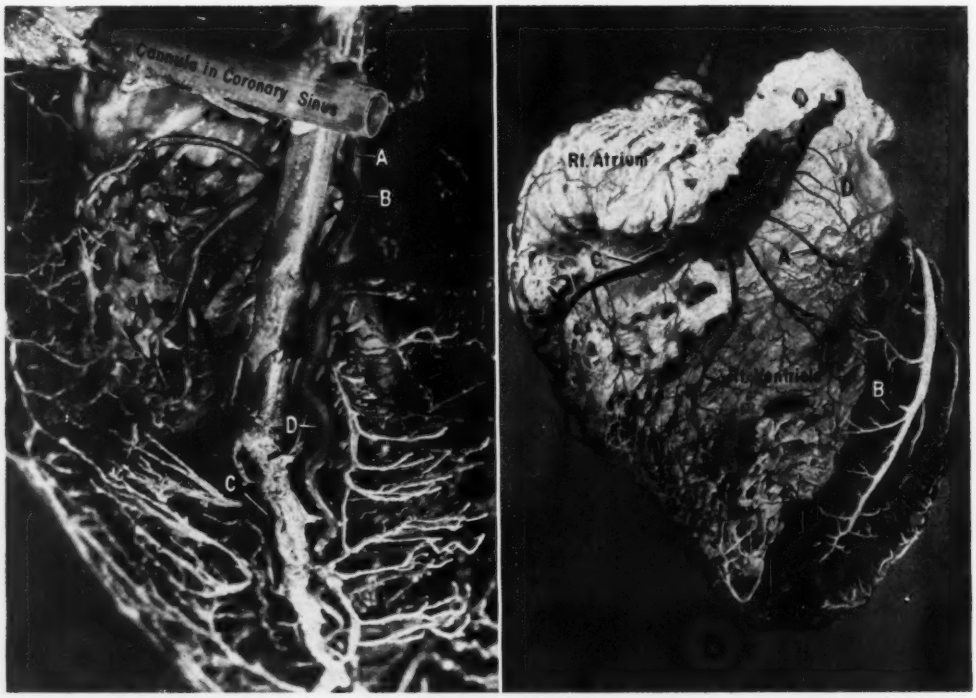

FIG. 4 *Left.* Photograph of the U-turn made by the right coronary artery beneath the posterior interventricular vein. (*A*) Branch to the atrioventricular node. (*B*) U-turn of the right coronary artery. (*C*) Posterior interventricular vein, which has been cannulated. (*D*) Posterior descending termination of the right coronary artery.

FIG. 5 *Right.* Photograph showing the anastomoses between the right coronary artery and left anterior descending coronary artery in the region of the main pulmonary artery and pulmonary conus. Note the proximity of the left anterior descending coronary artery to the edge of the cast of the right ventricular cavity near the apex, where it is viewed perpendicularly to the epicardium. The white vessels are veins. (*A*) The ring of Vieussens. (*B*) Left anterior descending coronary artery. (*C*) Right coronary artery. (*D*) Main pulmonary artery.

per cent was provided from the anterior descending artery.

Of this latter group of 12 hearts, the posterior descending artery of 2 of them was the termination of the left circumflex artery, so that the left coronary artery thereby supplied all the septum. In a third heart of these 12, the termination of the posterior descending branch of the right coronary artery was so poorly developed that it was distributed to only about 5 per cent of the interventricular septum.

The venous drainage of the ventricular septum was bidirectional. The larger and more numerous veins drained anteriorly into the left anterior interventricular vein; the remainder of the blood drained posteriorly into the posterior interventricular vein. Both of these channels emptied into the coronary sinus, although the juncture of the posterior interventricular vein was always extremely near the entrance of the coronary sinus into the right atrium. Unlike the coronary arteries, the veins communicated freely on the surface of the heart. For this reason, venous blood from the septum may sometimes reach the right anterior cardiac veins by way of branches of the left anterior interventricular vein and empty directly into the right atrium, separate from the coronary sinus.

Discussion

The blood supply of the human interventricular septum is vital for the maintenance of normal cardiac conduction. Since the septum contains the main trunks of the conduction system, interference with septal circulation, as from coronary occlusion, would be expected to result in defective conduction. Furthermore, cardiovascular operations involving the interventricular septum require familiarity with the vascular anatomy of this area.

The extent to which the blood supply of the human interventricular septum is derived from the left anterior descending coronary artery is not generally recognized. Since the thickness of the normal free left ventricular wall is approximately 12 mm. and since the posterior penetrating septal arteries (except near the atrioventricular node) rarely exceed 15 mm. in length, it seems highly unlikely that the septal branches of the posterior descending artery contribute a significant amount of blood to the ventricular septum. The greatest ultimate value of these posterior penetrating arteries may be as a source of potential collateral circulation.

In 41 of the 43 hearts in this study the posterior descending artery was the termination of the right coronary artery and supplied a significant portion of the posterior wall of the left ventricle. This finding differs from Schlesinger's description of the blood supply of this area, in which the right coronary was less important.[9]

The interventricular septum and its conduction system may be divided into 2 areas. The upper portion, which includes the atrioventricular node, the bundle of His, and the upper segments of the 2 main bundle branches, was supplied in 40 (over 90 per cent) of the hearts in this series by a branch of the right coronary artery that passed under the posterior interventricular vein (figs. 2 and 4). Embryologic significance of the course of this particular branch of the right coronary artery has been discussed previously.[8]

The second or lower area of the interventricular septum comprises the greater mass of the septum, including most of the 2 main bundle branches and the Purkinje arborization of the septum. This area was supplied mainly by penetrating branches from the left anterior descending coronary artery.

From this arbitrary division it is apparent that occlusion of the right coronary artery may be associated with disturbances in atrioventricular conduction (various degrees of block). Occlusion of the left anterior descending artery may produce bundle-branch block or free-wall ("arborization") block. These deductions depend upon the efficiency and extent of collateral circulation.

The potential channels for collateral circulation are most numerous in the interventricular septum. Communications in the septum afford collateral flow between the 2 major coronary arterial trunks to compensate for occlusion of either. How frequently the anastomoses described in this study will occur in the septum of any given human heart can, of course, only be conjectured; in general, however, the more satisfactory the casting was from a technical standpoint, the more numerous were the anastomoses demonstrated. In this study of normal hearts several from the third and fourth decades of life exhibited numerous areas of gross anastomosis.

Since penetrating branches from the left anterior descending coronary artery to the septum are always multiple (figs. 1 and 2), occlusion of one or more of these may well be responsible for some of the obscure clinical cardiac states such as "spontaneous" bundle-branch block or the electrocardiographic syndrome of septal fibrosis.[10]

The interesting observation that the anterior septal arteries travel initially near the right ventricular cavity may be related to the lower pressure in that chamber. The arteries supplying the free wall of the left ventricle also tend to remain away from the high pressure within that chamber, traversing the epicardium until they reach the area to be supplied with blood, whereupon they penetrate perpendicularly into the myocardium.

Summary

The blood supply of the human interventricular septum has been studied in 43 normal hearts prepared by injection of the vessels with vinylite, followed by corrosion of the tissues with concentrated hydrochloric acid. The major blood supply of the ventricular septum was found to be derived from diagonally penetrating arteries entering from the left anterior descending coronary artery. Branches from the posterior descending coronary artery supplied only a small zone of the ventricular septum near the posterior interventricular sulcus and the region of the atrioventricular node. The interventricular septum is an important site of collateral circulatory channels in the human heart.

Acknowledgment

We are grateful to Drs. William Eckert, Wallace Clark, and Nicholas Chetta for their assistance in this study.

Summario in Interlingua

Le provision de sanguine in le septo interventricular del homine esseva studiate in 43 cordes normal, preparate per (1) le injection de vinylite in le vasos e (2) le subsequente corrosion del histos per medio de concentrate acido hydrochloric. Esseva trovate que le major provision de sanguine in le septo interventricular es derivate ab arterias que penetra diagonalmente veniente ab le descendente arteria coronari sinistro-anterior. Brancas ab le posterior arteria coronari descendente alimentava solmente un micre zona del septo ventricular in le vicinitate del sulco interventricular posterior e in le region del nodo atrioventricular. Le septo interventricular es un sito importante de canales de circulation collateral in le corde human.

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The Concept of "Masquerading" Bundle-Branch Block

An Electrocardiographic-Pathologic Correlation

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VICTOR H. KUGEL, M.D., AND MAURICE LEV, M.D.

This is a clinicopathologic study of 2 patients who electrocardiographically presented so called "masquerading" bundle-branch block. The conduction systems and the entire hearts of these patients were studied pathologically by methods especially devised by Lev for electrocardiographic correlation. This report is part of a long-term project attempting to ascertain the anatomic substrate of electrocardiographic abnormalities.

THE electrocardiographic complex referred to as "masquerading bundle-branch block," consisting of the pattern of left bundle-branch block (LBBB) in the limb leads and right bundle-branch block (RBBB) in the unipolar precordial leads, has generated considerable speculation and interest relating to possible mechanisms responsible for its production. It has been designated "masquerading" by Richman and Wolff[1] because they thought that even though the precordial leads suggested RBBB according to Wilson's criteria (right precordial leads showing late R or R′ deflections, regardless of the morphology of the limb leads), this complex was actually the result of LBBB. This discrepancy was believed to be the result of the probable transmission of high septal potentials through the infarcted free right ventricular wall. These authors[1] described 4 such cases in which the vectorcardiograms were interpreted as LBBB. The vectorcardiograms obtained in their cases differed markedly from those usually seen in LBBB except for the initial vectors, which were thought to be typically suggestive of LBBB. The marked difference in the remainder of the vectorcardiogram was attributed to the complication of septal infarction. A postmortem examination was reported by these authors on a case in which extensive infarction of the interventricular septum and the posterolateral wall of the left ventricle was found. No histologic study of the conduction system was mentioned.

Sodi-Pallares and Rodríguez[2] in an earlier study on activation of the interventricular septum and the clinical evaluation of septal damage described this same electrocardiographic complex. In an effort to clarify this discrepancy between limb and precordial leads, they studied additional leads taken around the thorax at different levels searching for the electrocardiographic evidence of LBBB in these leads to conform with what the limb leads showed. In some of their cases this was found in leads taken in higher interspaces than the conventional chest leads. However, even here the precordial leads showed delayed intrinsicoid deflections over both the right and left precordial regions. The explanation offered was that the infarct had involved the lower portion of the interventricular septum and invaded the adjacent right and left free ventricular walls. The infarct then would extend in the septum to portions of the septum formed by the right ventricle and would only partially involve the portion formed by the left ventricle. The left intraventricular cavity potential would be that found in the presence of LBBB with the pattern varying, depending upon the orientation of the precordial elec-

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This investigation was supported by a research grant (H1187) from the National Heart Institute of the National Institutes of Health, U. S. Public Health Service.

trodes to the infarcted portions of the septum and left ventricle, producing an RS complex over infarcted areas and a broad notched R over portions of the left ventricle which were not infarcted or were not oriented toward the infarcted septum. Leads over the right ventricle would show a qR, qRR′, or RR′ complex, depending on their orientation to different portions of the septum. Despite the late R over the right precordial leads, these investigators thought that the lesion represented by the electrocardiogram was referable to LBBB rather than RBBB or bilateral BBB. In a subsequent paper from the same group (Rodríguez, Anselmi, and Sodi-Pallares[3]), the possibility of an alteration of conduction in both bundle branches is mentioned. This explanation, however, is discarded in favor of one explaining the findings on the basis of LBBB alone.

In a review of the literature, we could find no postmortem studies in these cases with detailed examination of the conduction system and a correlation of these findings with multiple unipolar precordial leads in addition to standard limb leads. We therefore studied 2 of our cases of the same type heretofore described, which had come to postmortem examination, utilizing the method of study of the conduction system and of the entire heart devised by Lev and his associates.[4-10] Vectorcardiograms were not done on these patients.

Materials and Methods

The electrocardiograms were taken with the Sanborn direct-writing electrocardiograph. Conventional standard limb leads, augmental unipolar extremity leads, and unipolar chest leads were routinely taken on both patients.

Each heart at autopsy was opened in the traditional manner along the course of the circulation, with the exception that the initial cut passed from the inferior vena cava through the right atrial appendage, thus sparing the sinoatrial (SA) node. The heart was then fixed in neutral formalin for 2 to 7 days, at the end of which time all chambers were photographed. The SA node and its approaches were then removed for serial sectioning, as previously published, and every twentieth section was retained. A second block was made from the right atrial appendage and the superior wall of the right atrium. This block contained the ramus ostii cavae superioris, the blood supply to the SA node. This block was cut serially and every eightieth section retained. The anterior and inferior walls of both atria and ventricles were then removed from the atrial and ventricular septa. The atrioventricular (AV) node, bundle, and bundle branches up to the region of the papillary muscles were then included in 5 blocks. The AV node and its approaches (including the blood supply—the ramus septi fibrosi) and the penetrating portion of the bundle of His were present in the first block and were sectioned serially, every twentieth section being retained. The branching portion of the bundle of His and the beginning of the right and left branches were present in the second block and were sectioned serially, and every fortieth section was retained. The remainder of the bundle branches up to the level of the papillary muscles of the left ventricle and the moderator band were found in the third, fourth, and fifth blocks and were sectioned serially, every fortieth section being retained. The remainder of the heart—the atrial septum, the most anterior part of the ventricular septum, the posterior ventricular septum, and the anterior and posterior walls of both atria and ventricles—were completely cut into blocks, and 2 sections were made from each block. Sections were cut at 6 or 7 microns. All sections were stained alternately with hematoxylin-eosin and Weigert-van Gieson stains. The number of sections thus obtained were 1,081 in case 1 and 854 in case 2.

Case Reports

Case 1. B. S., a 75-year-old white man was admitted to the hospital on November 28, 1954, for congestive heart failure. He was a known hypertensive patient for many years and for over 2 years had experienced angina. He denied knowledge and symptoms of a definite coronary thrombosis in the past. Prior to admission his angina increased in both frequency and severity with concomitant increase in his congestive heart failure and with an episode of protracted chest pain. Following admission to the hospital his course persistently worsened. Peripheral vascular collapse did not develop but he remained in congestive failure. His course was marked by cerebral vascular insufficiency. Treatment consisted of digitalis, oxygen, diuretics, and other supportive measures. Quinidine was employed because of frequent premature ventricular contractions. He suddenly died on December 2, 1954, the fourth hospital day.

The laboratory data were noncontributory except for 3+ albuminuria, a specific gravity of 1.010, and negative serologic tests.

Electrocardiographic Examination. Two electrocardiograms were available for study, one taken 1 month prior to admission and another 1 day after

admission. An electrocardiogram taken on October 26, 1954 (fig. 1), showed atrial fibrillation with ventricular premature contractions. The standard limb and unipolar extremity leads showed a LBBB configuration, whereas the precordial leads showed RBBB. The intrinsicoid deflection in V_1 was 0.12 second, and 0.06 second in aV_L. The QRS interval was 0.12 second. (There was infarction of the septum, anterior and posterior walls.) No true left ventricular leads were evident in the usual precordial locations and, unfortunately, no exploratory leads were taken. These electrocardiographic findings are consistent with RBBB, left ventricular hypertrophy, infarction of the septum and free walls of the left ventricle, and possibly right ventricular hypertrophy. An alternative interpretation is "masquerading" BBB.

An electrocardiogram taken on November 29, 1954, showed atrial fibrillation with ventricular premature contractions and LBBB pattern in standard limb and unipolar extremity leads. The QRS interval was 0.12 second. The intrinsicoid deflection in the right precordial leads was 0.12 and 0.06 second in aV_L. The interpretation is the same as for the previous electrocardiogram.

Postmortem Examination. Aside from the findings in the heart, the pathologic diagnoses were (1) arteriolar nephrosclerosis with arteriolar necrosis, (2) generalized arteriolar sclerosis with early necrosis, (3) chronic passive hyperemia of the lungs, liver and spleen, (4) bilateral bronchopneumonia, lower lobes, and (5) chronic cholecystitis with cholelithiasis.

Heart. Gross Examination. The heart weighed 630 Gm. The epicardium was somewhat puckered over the posterior wall of the left ventricle. The myocardium in this region was somewhat firmer than normal, and white streaking permeated this

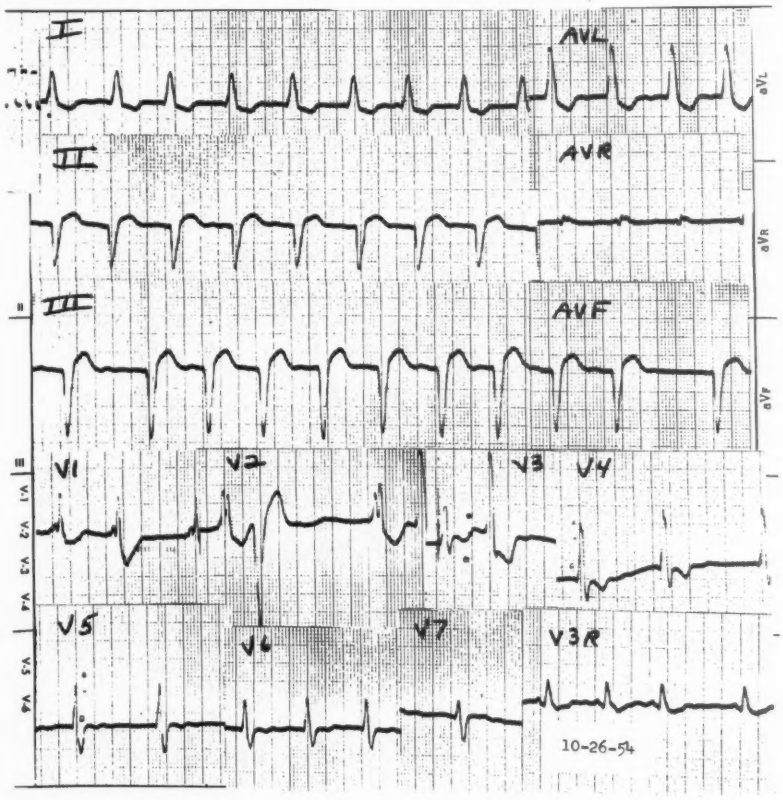

FIG. 1. Case 1. 10/26/54. Atrial fibrillation with premature ventricular contractions. LBBB in standard and unipolar extremity leads and RBBB in unipolar precordial leads. Intrinsicoid deflection is 0.12 second in V_1, 0.06 in aV_L. QRS duration is 0.12 second. Anteroseptal and posterior myocardial infarction.

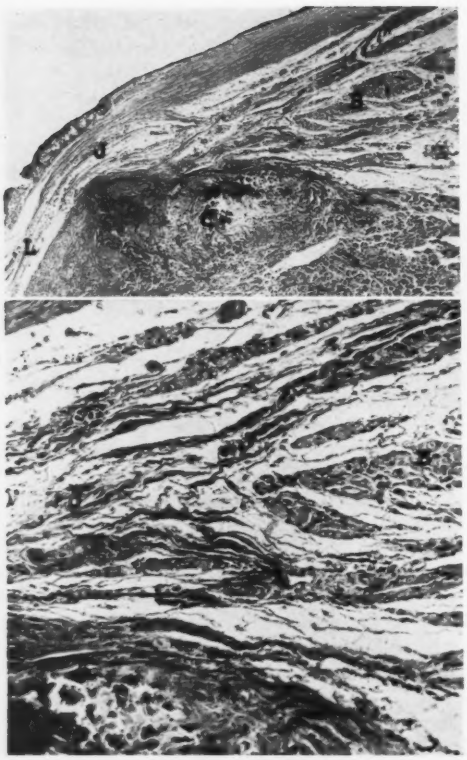

FIG. 2. Case 1. Atrioventricular bundle at origin of part of the posterior radiation, showing calcified mass in the upper part of the ventricular myocardium adjacent to the bundle and LBB. There is elastosis of the junction of the bundle and LBB. Weigert-van Gieson stain. *Top*, × 51; *Bottom*, × 170; *B*, atrioventricular bundle; *L*, LBB; *J*, junction region of the above; *C*, calcified mass.

region. Both the right and the left ventricles were markedly hypertrophied and dilated. It could not be ascertained whether dominant hypertrophy was present in either side. There was moderate sclerosis of the coronary arteries, with only slightly detectable narrowing.

Microscopic Examination. General Pathology. There was generalized arteriolar narrowing throughout the entire heart, accompanied by a mild form of acute vascular degeneration.

Pathology of Individual Chambers and Walls. The myocardium of the free walls of both atria showed slight fibrosis in many areas with additional acute degenerative changes in that of the left. The atrial septum showed no changes. Throughout the myocardium of the free walls of the left ventricle there was slight to moderate subepicardial and perivascular fibrosis with a dispersion of small microscopic scars and occasional organizing infarcts. These changes were most marked in the posterior wall. The posterior part of the ventricular septum was similarly markedly involved with a lesser involvement of the anterior part of the septum. The free walls of the right ventricle showed only occasional small scars with minimal fibrosis.

Pathology of the Conduction System. The ramus ostii cavae superioris showed no change. The ramus septi fibrosi showed slight narrowing. The *SA node* showed degeneration of occasional isolated fibers. At the approaches to the SA node, the posterior crest and other atrial musculature presented slight to moderate fibrosis with an occasional small scar. The approaches to the AV node showed slight to moderate fibrosis. The *AV node* presented no change. The *penetrating portion of the bundle of His* presented a small scar near its termination. The *branching portion of the bundle of His* at its bifurcation showed elastosis and compression by a calcified mass in the adjacent ventricular musculature (fig. 2). *Right bundle branch* (fig. 3*A, B*): Close to its origin, there was marked fibrosis which diminished somewhat up to the region of the muscle of Lancisi. In addition, this segment showed some acute degenerative changes. Distal to the muscle of Lancisi the fibrosis became more marked, amounting at 1 point to about four-fifths replacement of the bundle branch. The process again diminished to be followed by almost complete replacement by connective tissue. The most distal portion and the divisions of the moderator band were not available for study. *Left bundle branch* (fig. 3*C, D*): There was calcification of the septum adjacent to, but not involving, the beginning of the LBB. Slight fibrosis was focally present throughout. In addition, in the upper portion there were mild acute degenerative changes with a scattered infiltration of lymphoid cells. In the distal portion there was an increase in the extent of the acute degenerative changes, accompanied by fatty infiltration and a fine dispersion of round cells.

Pathologic Diagnoses of the Heart. (1) Marked hypertrophy of the right and left ventricles, (2) arteriolosclerosis of the myocardium with superimposed mild acute vascular degeneration, (3) diffuse fibrosis with small scars of the myocardium, with maximal involvement of the posterior part of the ventricular septum and posterior wall of the left ventricle, (4) elastosis and compression of the common bundle at its bifurcation, (5) marked fibrosis of the RBB and slight fibrosis of the LBB, and (6) focal acute degenerative changes of the ventricular myocardium and the right and left bundle branches.

Electrocardiographic-Pathologic Correlation. In

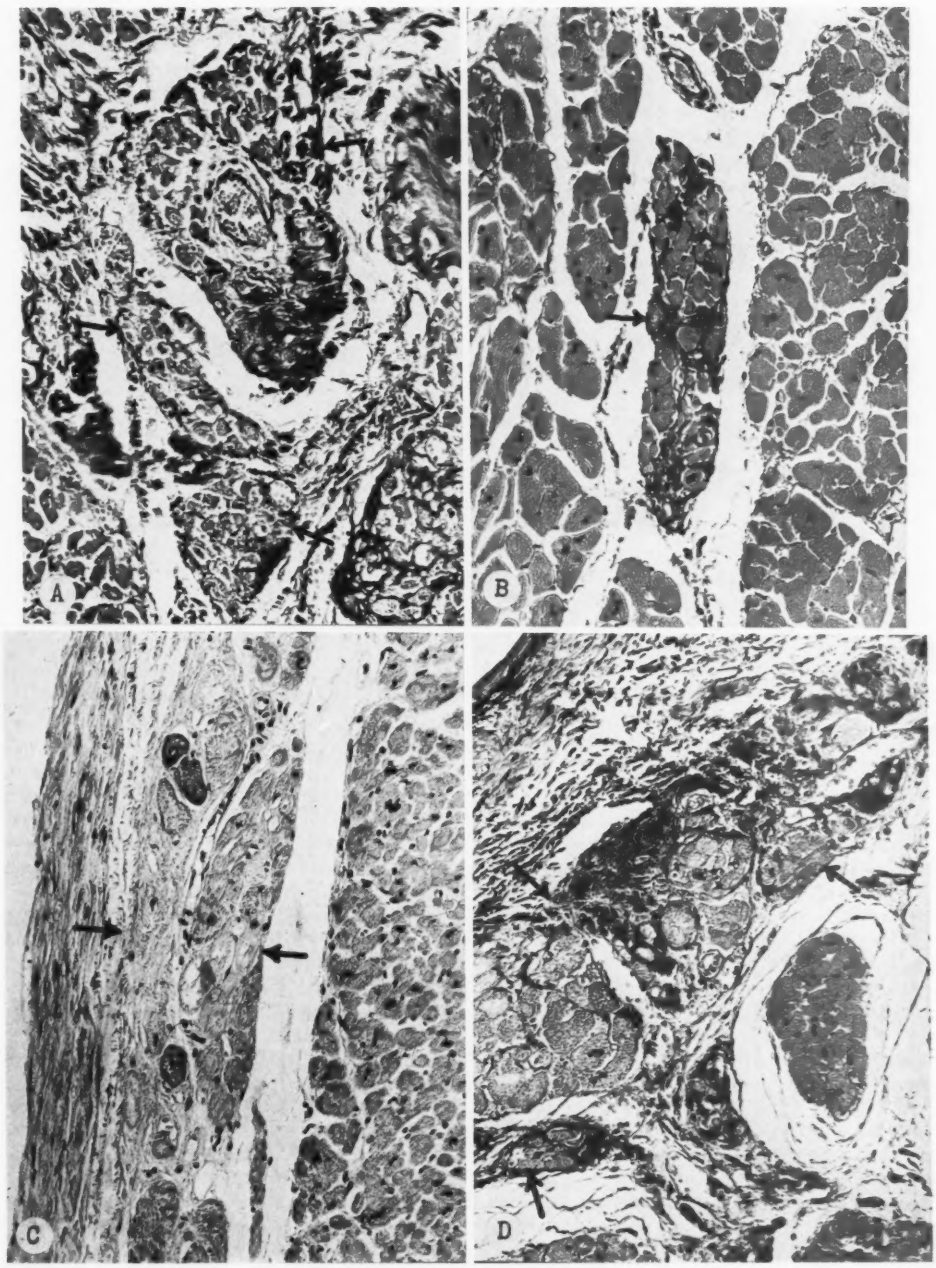

FIG. 3. Case 1. Bundle branches showing marked fibrosis, but not complete obliteration of RBB, and fibrosis and acute degenerative changes in LBB. *A*, RBB, first portion. Weigert-van Gieson stain. × 170. *B*, RBB, intramyocardial portion. Weigert-van Gieson stain. × 170. *C*, LBB. Hematoxylin-eosin stain. × 170. *D*, LBB, peripherally. Weigert-van Gieson stain. × 170. Arrows point to the respective bundles.

a patient with hypertensive and arteriosclerotic heart disease, electrocardiographic findings suggested septal infarction with involvement of the free walls of the left ventricle, and there was an electrocardiographic pattern of LBBB in the limb leads and RBBB pattern in the precordial leads. Autopsy findings revealed hypertensive and arteriolosclerotic heart disease with generalized fibrosis and small scars involving maximally the posteroseptal wall of the left ventricle, elastosis and compression of the atrioventricular bundle at its bifurcation, marked fibrosis of the RBB, and slight fibrosis of the LBB.

Case 2. S. A., a 61-year-old male carpenter, was initially hospitalized on November 14, 1949, because of exertional dyspnea of 6 months' duration.

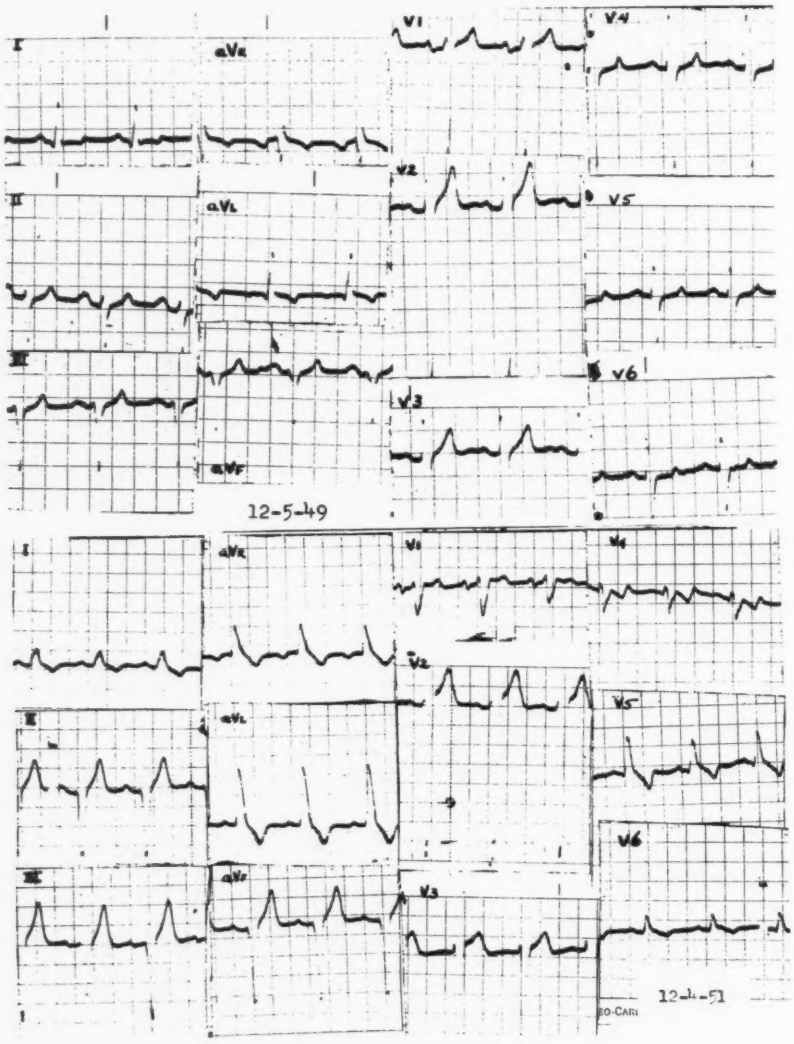

FIG. 4 *Top.* Case 2. 12/5/49. Normal sinus rhythm. Left ventricular hypertrophy. QRS duration 0.10 second, P-R 0.19 second.

FIG. 5 *Bottom.* Case 2. 12/4/51. Normal sinus rhythm. QRS 0.13 second. Q wave has disappeared in L_1 and aV_L. Change from previous tracing demonstrating intraventricular conduction defect of LBBB configuration.

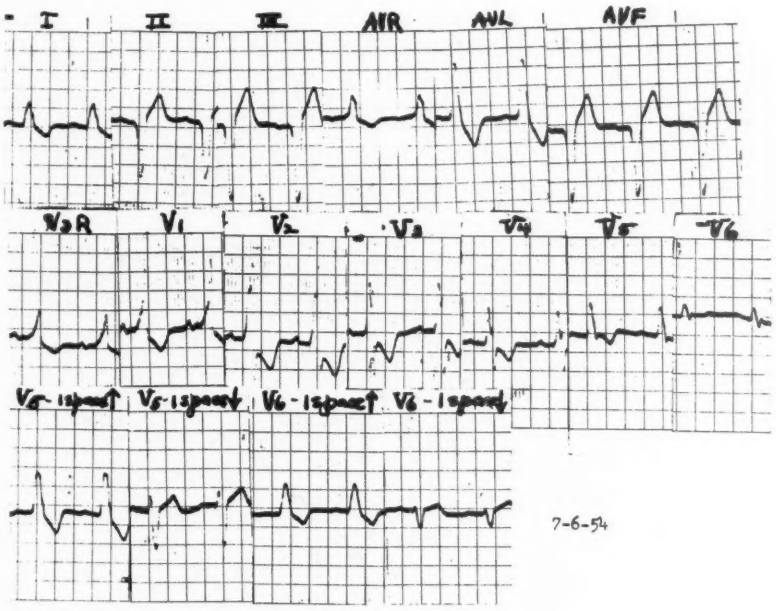

FIG. 6. Case 2. 7/6/54. Normal sinus rhythm. P-R interval 0.19 second. QRS 0.14 second. RBBB noted in right precordial leads and LBBB in standard and unipolar extremity leads. Intrinsicoid deflection is 0.11 second in V_1 and 0.12 second (second peak) in V_6.

On admission, his blood pressure was 230/120 and there were findings of congestive heart failure. He was discharged 1 month after admission, on digitalis, after diagnoses were made of arteriolonephrosclerosis, hypertensive heart disease with left ventricular hypertrophy and congestive heart failure. The patient was readmitted on April 28, 1951, because of recurrent cardiac insufficiency. There was no interim history of precordial distress. The blood pressure was 250/120 and the physical findings included those of right- and left-sided heart failure. He was treated as in his previous admission, losing 22 lb. in 2 months. The patient had 2 subsequent hospital admissions on November 11, 1951, and July 2, 1954, for recurrent symptoms of congestive failure with clinical evidence of severe failure and moderately severe hypertension. The heart showed progressive enlargement to an extremely large size. His fifth and final admission on October 1, 1954, was for intermittent epigastric pain associated with vomiting. On examination, in addition to severe congestive failure, he showed evidence of a perforated abdominal viscus and massive atelectasis of the right lung. Because he was a poor surgical risk, he was treated with Wangensteen suction and a Cofflator. The right lung re-expanded, but the patient lapsed into coma and died on the sixth hospital day. No history of angina could be obtained after repeated questioning.

Pertinent laboratory data during the long period of observation included a positive blood Kahn test (less than 10 units), hyposthenuria, and moderate retention of urea nitrogen. A benzodioxane test was negative for evidence of pheochromocytoma.

Electrocardiographic Examination. An electrocardiogram taken December 5, 1949 (fig. 4), on the first hospital admission showed a normal sinus rhythm and suggestive evidence of left ventricular hypertrophy. The QRS interval was 0.10 second and the P-R interval was 0.19 second.

An electrocardiogram taken on December 4, 1951 (fig. 5), on the third hospital admission, showed a normal sinus rhythm, P-R interval of 0.20 and QRS of 0.13 second. The Q wave had disappeared in lead I and aV_L. A change from the previous tracing was noted, with development of an intraventricular conduction defect of LBBB configuration.

An electrocardiogram taken July 2, 1954, on the fourth hospital admission, showed a normal sinus rhythm, P-R interval of 0.20 and QRS of 0.13 second. RBBB configuration was now present in the right precordial leads and LBBB configuration in the standard and unipolar extremity leads. The intrinsicoid deflection was 0.12 second in V_1 and V_6.

An electrocardiogram taken July 6, 1954 (fig. 6), showed a normal sinus rhythm, P-R interval of 0.19 second and QRS of 0.14 second. RBBB was present in right precordial leads and LBBB in standard and unipolar extremity leads. The intrinsicoid deflection was 0.11 second in V_1 and 0.12 second (second peak) in V_6. There was no diagnostic electrocardiographic evidence of myocardial infarction.

Postmortem Examination. Aside from the findings in the heart, the pathologic diagnoses were (1) chronic passive hyperemia of the lungs with pulmonary edema, (2) chronic ulcer of the stomach with perforation, (3) fatty metamorphosis of the liver with periportal fibrosis, (4) congenital absence of the right kidney, (5) arteriolosclerosis of the left kidney with nephrosis, (6) ascites, (7) icterus, and (8) cyanosis.

Heart. Gross Examination. The heart weighed 950 Gm. Both ventricles were markedly hypertrophied, the left, however, dominantly so. Both atria shared in the hypertrophy. The anterior descending coronary artery coursed deep into the ventricular myocardium. There was only minimal sclerosis of the coronary arteries, and no narrowing.

Microscopic Examination. General Pathology. There was diffuse arteriolosclerosis with acute vascular degeneration, with associated degenerative and inflammatory changes in collagen and fat tissue.

Pathology of Individual Chambers and Walls. The myocardium of the free walls of the atria and the atrial septum showed diffuse fibrosis, which was more marked on the right side. The myocardium of the free walls of the left ventricle, the ventricular septum and the anterior wall of the right ventricle showed marked fibrosis with microscopic scars. This was more marked in the inner two-thirds of the walls. Subepicardially, there were also acute degenerative changes in the myocardial fibers. The posterior wall of the right ventricle showed similar slight changes.

Pathology of the Conduction System. There was no narrowing of the ramus ostii cavae superioris. The *SA node* showed no change. The approaches to the SA node showed considerable fibrosis, with acute degenerative changes of the myocardial fibers. The approaches to the AV node showed acute degeneration of the fat tissue with focal infiltration of macrophages. The *AV node* was normal. The *penetrating portion of the AV bundle* showed the above-mentioned changes in the associated fat and collagen. The *branching portion of the bundle* showed marked elastosis and what appeared to be compression at the bifurcation. *Right bundle branch* (fig. 7*A, B*): At the origin, there was slight fibrosis. This became progressively more marked at the muscle of Lancisi, so that at one point it was considerably replaced by connective tissue. In addition, focal acute degenerative changes were noted in this portion. Distal to the muscle of Lancisi, the bundle branch lay in a scar where at one point it was markedly, but not completely, replaced. It then was the seat of moderate fibrosis, which was present until its termination. Here it was surrounded by collagen and fat showing degenerative changes. The most distal part of the moderator band and its branches were not available for study. *Left bundle branch* (fig. 7*C, D*): There were fibrosis and compression at the beginning of the LBB, which persisted focally more distally. In addition, there were collagen and fat changes around the fasciculi, with focal degeneration of some of the bundle fibers.

Pathologic Diagnoses of the Heart. (1) Massive hypertrophy of the heart (left ventricle maximal, right ventricle marked, both atria marked), (2) intramyocardial course of the left anterior descending coronary artery, (3) marked arteriolosclerosis with acute vascular and perivascular degeneration, (4) marked fibrosis of the myocardium with small scars involving the septum, the anterior and posterior walls of the left ventricle, and the anterior wall of the right ventricle maximally, the right atrium moderately, and the left atrium, atrial septum, and the inferior wall of the right ventricle slightly, (5) compression and elastosis of the bundle of His at its bifurcation, and marked fibrosis of the RBB with moderate fibrosis of the LBB, (6) focal acute degenerative changes of the right and left bundle branches.

Electrocardiographic-Pathologic Correlation. In a patient with syphilis, a peptic ulcer and hypertensive heart disease, the electrocardiographic diagnosis was left ventricular hypertrophy, and there was an electrocardiographic pattern of LBBB in the limb leads and delayed intrinsicoid deflections over both the right and left chest leads. Autopsy findings revealed hypertensive and arteriolosclerotic heart disease with massive left ventricular hypertrophy and marked right ventricular hypertrophy, marked fibrosis with small scars of the entire left ventricle and anterior wall of the right ventricle, with less marked involvement of the inferior wall of the right ventricle, elastosis of the atrioventricular bundle at its bifurcation, marked fibrosis of the RBB, and moderate fibrosis of the LBB.

Discussion

The electrocardiograms in our cases disclosed LBBB in the limb leads and RBBB in the precordial leads. Case 2, which showed LBBB in the extremity leads and delayed intrinsicoid deflections over the right and left

precordial regions, points up the value of exploring the left precordial area in cases of this type in search for left ventricular potentials. In these cases the usual chest leads may

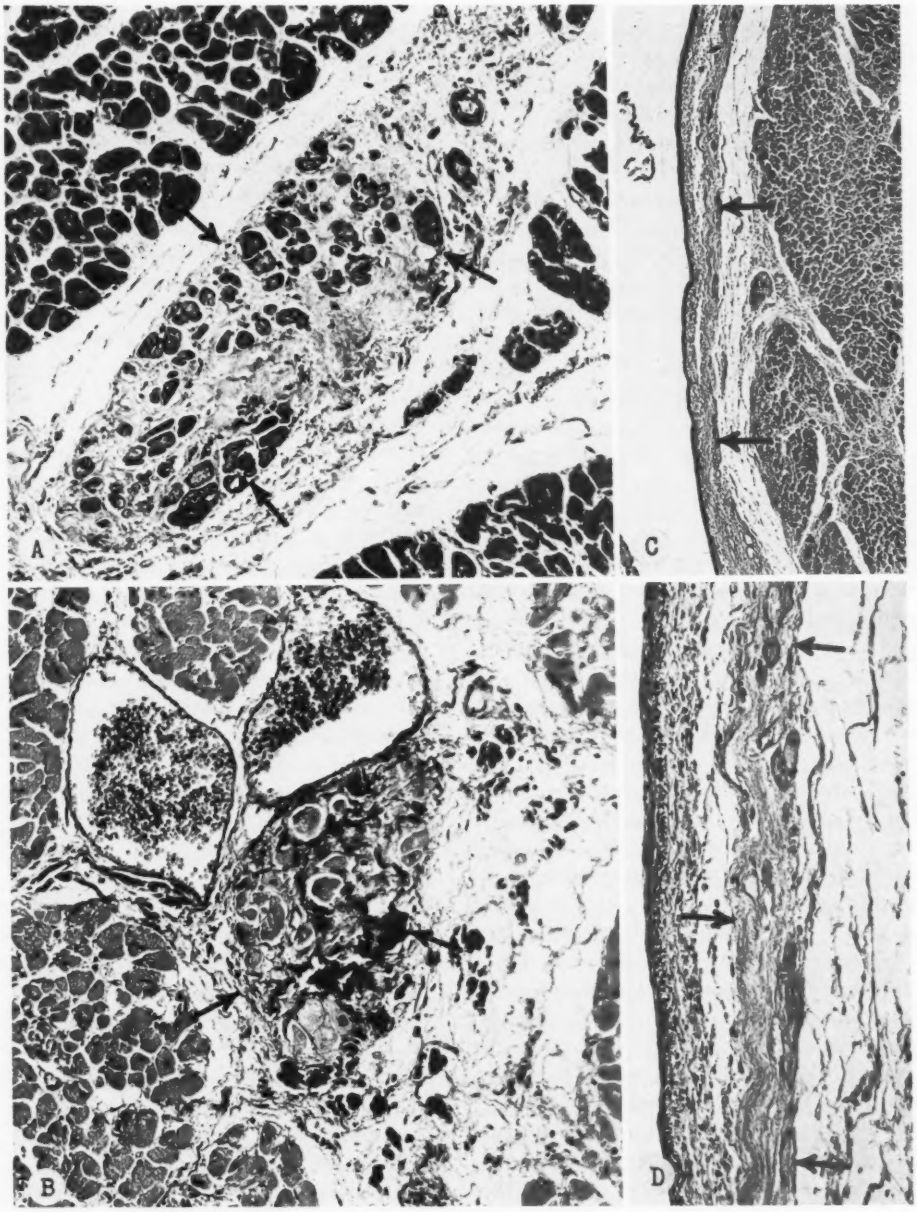

FIG. 7. Case 2. Bundle branches, showing marked fibrosis of RBB, and zone of marked fibrosis of LBB, in addition to acute degenerative changes of RBB. *A*, RBB, intramyocardial portion, proximal. Hematoxylin-eosin stain. × 170. *B*, RBB, intramyocardial portion, distal. Weigert-van Gieson stain. × 170. *C*, LBB in the upper portion. Hematoxylin-eosin stain. × 51. *D*, LBB. Hematoxylin-eosin stain. × 170. Arrows point to the respective bundles.

TABLE 1.—*Degree of Pathologic Involvement*

	Case 1	Case 2
SA node	±	−
Blood supply to SA node	−	−
Approaches to SA node	+	+2
Right atrium	+	+2
Left atrium	+	±
Approaches to AV node	+	±
AV node	−	−
Blood supply to AV node	±	−
AV bundle, penetrating	±	±
AV bundle, branching	+	+
Right bundle branch	+3	+3
Left bundle branch	+2	+2
Left ventricle, anterior wall	+2	+3
Left ventricle, posterior wall	+3	+3
Right ventricle, anterior wall	±	+3
Right ventricle, posterior wall	±	+
Atrial septum	−	+
Ventricular septum, anterior	±	+3
Ventricular septum, posterior	+3	+3
Perforating arteries	+2	+2
Hypertrophy, left ventricle	+4	+4
Hypertrophy, right ventricle	+4	+3

be oriented to an infarcted portion of the left ventricle and septum, and could reflect transeptal potentials originating in the right ventricular cavity, thereby failing to reflect the depolarization process in the left ventricle.

The pathologic lesions that were found to be common to our cases are (table 1) (1) incomplete, widespread damage to both the right and left bundle branches, (2) marked damage to the septal myocardium and the free walls of the left ventricle, and (3) marked hypertrophy of both ventricles. In an attempt to correlate the electrocardiographic findings of "masquerading" BBB with the pathologic findings, we must consider first those electrocardiographic changes that have been found to be associated with bilateral bundle-branch lesions at autopsy.[11-22] These are LBBB alone, RBBB alone, bilateral partial BBB, "unstable" BBB, and complete heart block. In LBBB, the RBB is normal or shows fewer changes than the opposite branch. In RBBB, the LBB is normal or presents fewer changes than the opposite branch. In bilateral and "unstable" BBB, the lesions are severe in both branches.

In our cases, the lesions were considerable in both branches, and perhaps more severe in the right than in the left bundle branch. However, we believe that it is difficult to equate lesions in two so completely different anatomic structures as the left and right bundle branches. Therefore it is unsafe to speak of preponderance of change on either side unless the difference is very marked. Since this degree of difference was not present in our cases, we can only say that we have considerable, but incomplete, lesions in both bundle branches. Hence, from the point of view of lesions in the conduction system, our cases fall more into the category of bilateral or "unstable" BBB, rather than in those of right or left BBB alone. However, our findings do not rule out the latter 2 possibilities from the physiologic or electric point of view.

We are, of course, cognizant of the fact that factors other than changes in the conduction system may be related to the electrocardiographic patterns in BBB.[23-28] Thus, the findings of hypertrophy of both ventricles, and the marked pathologic change in the septum in our cases, may prove to be of significance. It is to be noted that our study does not include examination of the nerves of the conduction system and of the heart, which may have a bearing on this problem.[27] Thus, a definitive statement as to the pathologic basis of this pattern must await completion of further studies of the anatomic base of right and left BBB, and of right and left ventricular hypertrophy, and of alterations in the conduction system without electrocardiographic evidence of conduction disturbances.

It is of interest that both of our cases were associated with ischemic changes related to arteriolar narrowing only. BBB and bundle-branch lesions associated with coronary arteriolosclerotic heart disease have previously been described by Evans and Turnbull,[13] and merit re-emphasis.

Hence we subscribe to the thesis that "masquerading" BBB is a type of bilateral BBB. Recently, Rosenbaum and Lepeschkin[29] have dealt with the problem of bilateral BBB from the clinical, electrocardiographic, and

physiologic points of view. They stated that a definite diagnosis of bilateral BBB can be made from electrocardiograms in which changes in the comparative degree of the block in the 2 branches allow the patterns of RBBB and LBBB to appear alternately, intermittently, or simultaneously in the same patient. They reiterate the contention that true partial bilateral BBB must prolong the atrioventricular conduction time. The intrinsicoid deflection is delayed only over the ventricle corresponding to the branch showing the greater degree of block and is within normal limits over the opposite chamber. The form of the QRS in bilateral BBB is determined by the branch that shows the greater degree of block, with the delayed conduction in the other branch not affecting the shape of the QRS, but acting by prolonging atrioventricular conduction. Where prolonged atrioventricular conduction does not occur, they believe the bundle branch on one side is associated with intraparietal block of the contralateral ventricle. Accordingly, they would interpret case 2 as unilateral BBB with contralateral intraparietal block, while case 1, in which atrial fibrillation was present, and the time of atrioventricular conduction hence unknown, they would interpret as bilateral partial BBB. Despite the absence of disturbances of atrioventricular conduction, we prefer our interpretation of partial bilateral BBB, because of the considerable pathologic changes in both bundle branches. However, here again further work must be done on the anatomic substrate of electrocardiographic disturbances to resolve this point.

The concept of Richman and Wolff[1] that LBBB alone exists in these cases is not ruled out by our pathologic findings as detailed above, but it is difficult to reconcile with the marked changes in the RBB. The explanation of Sodi-Pallares and Rodríguez that the electrocardiographic pattern is related to infarction involving the lower portion of the interventricular septum and the adjacent free walls of both right and left ventricles, and dominantly affecting the right ventricular portion of the septum, is not completely borne out by our pathologic findings. As pointed out above, the free walls of the right ventricle were significantly affected in only 1 of our cases.

Since neither of our cases showed complete destruction of either the right or left bundle branches, it would appear, from the standpoint of anatomic continuity, that both bundle branches could still function. This, however, does not presume to indicate the physiologic state or degree of responsiveness of the bundles. Unfortunately, we did not obtain vectorcardiograms on these patients, nor simultaneous chest leads, so that we cannot decisively indicate the direction of the initial electric forces and the dominant path followed by the electric impulse in the myocardium.

Several theoretic possibilities should be considered. Bilateral partial delay in both branches can produce the following electrocardiographic effects: 1. The pre-existing P-R interval can be lengthened without showing any evidence of RBBB or LBBB if the degree of delay in both branches is not too divergent. In this situation the bilateral partial BBB will be manifested by the prolonged atrioventricular conduction time, and the presence and extent of ventricular myocardial damage might be otherwise obscured. 2. If the block in the RBB is "complete" or almost complete, the electrocardiogram may show the pattern of RBBB, the LBBB manifesting itself in terms of lengthening of the pre-existing P-R interval. It is to be noted that in case 2, with a P-R of 0.20 second, there were considerable lesions of both bundle branches. It is also to be noted that in this case the P-R interval showed an insignificant increase from 0.19 to 0.20 second over the course of 4 years, whereas the serial electrocardiograms showed progressive development of LBBB in the limb leads and delayed intrinsicoid deflections in both right and left precordial leads. 3. A pattern of complete LBBB might occur when only partial block exists, due to the greater delay in activation of one ventricle while there is significantly less delay in the conducting system of the other ventricle. 4. Mahaim's paraspecific fibers[15, 30-32] arising from the atrio-

ventricular bundle and the LBB, might be functional or become so as a result of irritative disease processes. If these fibers would permit the wave of activation to bypass the bundle branches, then the electrocardiogram or the vectorcardiogram could not specifically determine the physiologic responsiveness of the right and left bundle branches and the route of activation. 5. The concept accepted by Rosenbaum and Lepeschkin[29] that RBBB plus focal or parietal block in the left ventricle can produce an electrocardiographic pattern indistinguishable from partial bilateral BBB may pertain in some cases.

It can be seen from the foregoing that the determination of the predominant pathway of activation in the cases considered in this report cannot be derived from the anatomic findings in our present state of knowledge. What requires reemphasis, is that this type of electrocardiographic complex signifies extensive myocardial damage, and with it bilateral involvement of the bundle branches. This study serves to point up the need for complete examination of all parts of the conducting system and the myocardium in order to establish a firm anatomic base for clinical electrocardiography.

Summary

1. Two cases having the features of "masquerading" bundle-branch block were subjected to careful histologic study of the entire heart, including the conduction system. In each instance, bilateral bundle-branch lesions of considerable intensity, which did not completely disrupt the continuity of the branches, were demonstrated.

2. Each case revealed extensive destruction of the interventricular septum, the free walls of the left ventricle, and marked bilateral ventricular hypertrophy.

3. In both of our cases the vascular changes in the heart were those of diffuse arteriolosclerosis.

4. It is suggested that this electrocardiograph complex is the result of partial bilateral bundle-branch block.

5. It is further suggested that the concept of "masquerading" bundle-branch block be discarded.

Acknowledgment

Acknowledgment is made to Paul Marvan, B.S., M.T. (A.S.C.P.) for his technical assistance.

Summario in Interlingua

1. Duo casos con le aspectos de "mascarada" de bloco de branca esseva subjicite a un meticulose studio histologic del corde integre, incluse le systema de conduction. Esseva demonstrate in ambe casos lesiones bilateral de branca de fasce que habeva attingite un intensitate considerabile sed que non disrumpeva le continuitate del brancas completemente.

2. Ambe casos revelava extense grados de destruction del septo interventricular e del pariete libere del ventriculo sinistre e marcate grados de bilateral hypertrophia ventricular.

3. In ambe nostre casos le alterationes vascular in le corde esseva le alterationes de diffuse arteriolosclerosis.

4. Es suggerite que iste complexo electrocardiographic es le resultato de bilateral bloco de branca.

5. Es etiam suggerite que le concepto del "mascarada" de bloco de branca sia abolite.

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Physical Factors in the Progression of Stenotic Vascular Lesions

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An explanation of the progression of stenotic lesions was sought in animal experiments. After surgical decrease of the lumen of arteries, progressive ingrowth of fibrous connective tissue led to the development of stenosis with changes in the artery that resembled those of coarctation. These changes are explained by the action of local blood pressures. Phenomena such as progressive stenosis, valvulogenesis, patterns of lipid infiltration, medial hypertrophy, thinning, and cystic change are discussed in terms of the concepts derived from these studies.

THE high pressure cardiad to stenotic arterial lesions, as for example in coarctation of the aorta and in closure of vital vessels such as the coronary arteries, is often sufficient to cause vascular injury with the production of aneurysms and rupture of the vessel wall.[1] Paradoxically, these continuously high arterial pressures never dilate the constricted arterial ring and relieve the stenosis.

The same paradox holds for stenotic lesions of the cardiac valves. Thus, in aortic or pulmonic valvular stenosis, the hypertrophied ventricle generates high pressures that beat recurrently against the contracted outlet; yet the stenosis is inexorably progressive, leading ultimately to cardiac failure.[2, 3]

These anomalous situations have been highlighted recently by repeated demonstrations that gentle digital dilation of stenotic mitral valves is sometimes sufficient to free the agglutinated leaflets and lead to clinical relief from the symptoms of obstructed blood flow. It is remarkable that the continuous action of the relatively high atrial pressure never achieves the same dilating effect as the momentary insertion of the surgeon's finger.

The mechanisms responsible for the development, persistence, and progression of these stenotic lesions have been ascribed to "congenital"[4] or "inflammatory"[5] processes. Unfortunately neither of these etiologic mechanisms is subject to adequate experimental analysis.

Other factors, such as mechanical forces may also participate in the initiation and progression of stenosis. These forces can be analyzed relatively easily to determine their potential influences on elastic or deformable vessels. Thus, flow can generate forces that cause the walls of elastic channels to be drawn together, producing a sharply reduced flow.[6] In other experiments[7] the flowing stream regularly induced stenosis of channels lined with silicone sometimes forming valves, coarctations, stenoses, dissections, and other arrangements strikingly similar to those of the cardiovascular system. These structural modifications have been shown to result from the pressure effects produced by high velocities of flow at a given point in the channel.

In the present study on animals, deviations of the blood streamlines are shown to induce the progression of stenotic lesions, with the production of valve-like structures and other modifications of the blood vessel wall. These

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Aided by grants H-690 and H-2271 from the National Heart Institute of the U. S. Public Health Service.

Presented in part at the Nineteenth International Physiological Congress, Montreal, Proc. Int. Physiol. Cong. 19: 710, 1953, and at the Second World Congress of Cardiology, Washington, D. C., Proceedings 2: 50, 1954.

FIG. 1. Technic of placement of tuck in the wall of aorta, permitting a portion of the circumference of the vessel to be free of manipulation. In some instances the tuck was placed on the subclavian artery.

effects appear to result from the response of the structures of the vessel to the local pressure acting on its walls.

METHODS

In preliminary experiments an encircling silk or linen ligature was used to constrict the thoracic aorta in 6 dogs. A slight proliferation of the intima with the production of a ring-like thickening was observed at the site of narrowing. Similar findings leading to nearly complete obstruction were described nearly 50 years ago by Halsted.[3] Since these changes could be attributed to injury of the vessel wall by the circumferential ligature, the procedure was modified to reduce the element of direct local injury.

In the experiments reported below, the cross section of the lumen was diminished by placing a mattress suture of linen or catgut in an arc of the vessel wall. Care was taken not to injure the portion of the wall not involved by the suture material (fig. 1). Sutures were placed in the descending thoracic aorta of 70 chicks and in the subclavian artery of 10 dogs. After periods of time up to 1 year, the animals were sacrificed and the heart and blood vessels were examined.

RESULTS

Effect of Slight Reduction in Lumen. In 15 experiments a suture was placed through a small arc of the blood vessel wall involving less than 25 per cent of the cross-section area. Examination at necropsy in periods up to 4 months revealed a small scar at the suture site as expected, but no significant changes were present in the remainder of the vessel wall.

These studies showed that the simple placement of the foreign material caused no significant change in the general structure of the vessel except for the local distortion, injury, and reaction.

Greater Degrees of Narrowing. In 55 chicks the cross section of the aorta was reduced by approximately half or more. Examination within a day or 2 after surgery in 4 chicks showed no notable changes in the vessels, beyond those directly due to the surgery itself.

Autopsy at periods of 1 week to several months after surgery revealed in most of the specimens that the suture had resulted in an isolated, nonproliferative scar, similar to those seen when only a small arc of the vessel was pinched off, as noted above.

However, in 17 chicks striking changes were seen at the site of the surgical narrowing. In general these consisted of a grossly visible ingrowth of tissue into the lumen of the vessel, immediately distal to the site of the placement of the suture. In some animals the vessel lumen was almost completely occluded by a diaphragm-like structure (figs. 2 and 3).

Gross examination revealed that the apparent diaphragm in some specimens was so thin as to be nearly translucent. In others a thick wall was present with only a tiny lumen remaining, usually in the center of the ingrowth. The growth varied from specimen to specimen and was not uniform, except for the generally marked tendency to proliferation into the lumen of the vessel.

FIG. 2 *Top.* Subclavian artery of a dog, partially constricted by a tuck 2 months before sacrifice. Cardiad side of the specimen (*left*); cross section at the level of greatest narrowing of the artery (*right*).

FIG. 3 *Bottom.* Subclavian artery of a dog partially constricted 4 months prior to sacrifice. Cardiad portion of the artery showing a coarctation-like stenosis (*right*). Cephalad end of the same specimen (*left*). The small central lumen is seen.

Microscopic examination of specimens taken at sacrifice 2 to 6 weeks after placement of the tuck revealed that the obstructing diaphragm consisted of young connective tissue with little or no collagen. The *intima* was not uniformly developed but consisted of relatively loose connective tissue, sometimes in large masses, and in other sites consisting of tag-like excrescences. The growth was definitely present in sites away from the suture material (figs. 4 and 5). There was no evidence that these structures were due to a previous local thrombosis, since blood pigment was not present. In no instance was the lumen completely

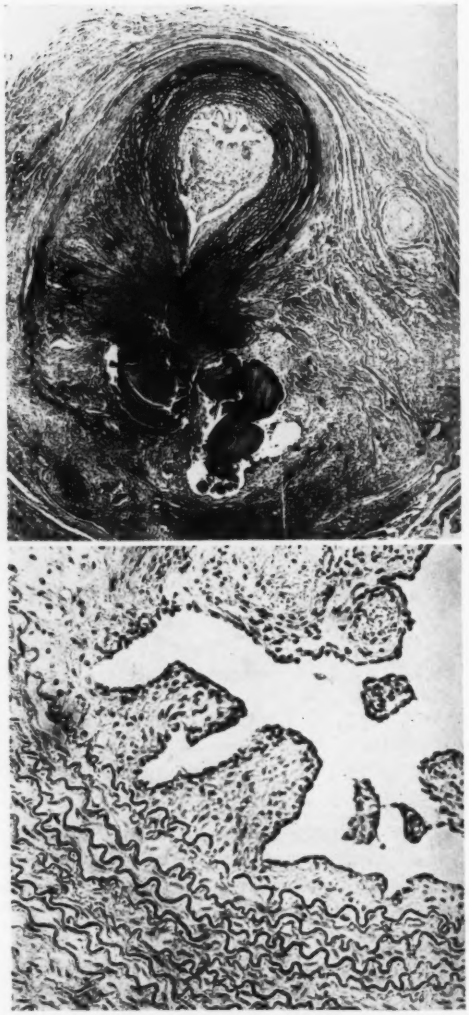

FIG. 4 *Top.* A chick aorta after partial narrowing by a tuck of catgut 3 weeks previously (Weigert stain). The catgut, with a marked inflammatory reaction, is still seen at lower portion of figure. The remaining lumen contains an ingrowth of intimal connective tissue. This comprises a central mass as well as small tags that have their origin on the portion of the wall not directly involved by the suture.

FIG. 5 *Bottom.* Microscopic section of a segment of the wall adjacent to section shown in figure 4. Finger-like projections of hyperplastic intima consisting of oval to spindle-shaped fibroblasts are seen. The surface is lined by endothelial cells. An occasional mononuclear cell is seen. Large cells with vacuolated cytoplasm are present. Hematoxylin and eosin. × 430.

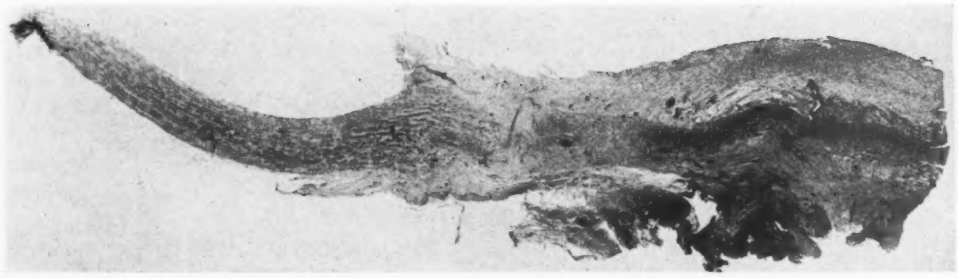

FIG. 6. A longitudinal section of a chick aorta showing the thickened cardiad portion above with intimal and medial thickening. The original site of the removed suture material is seen as clefts in the intimal-medial border and in the adventitia in the right third of the specimen. The tissue protruding to the top, which bears a superficial resemblance to a valve-like structure, was part of a diaphragm-like growth in the fresh specimen. At the site of the protuberance into the lumen, a reorganization of direction of the medial elastic fibers can be discerned. The thin vessel wall and the lack of intimal prolifieration beyond the site of narrowing are evident.

losed; a small orifice could always be seen.

At the site of the tuck an inflammatory round-cell infiltration and organization was present around the suture material, particularly within the first week or 2. In other specimens, the local inflammatory reaction had subsided.

The media in the regions not involved by the suture also showed changes. In some aortas there was an apparent change in the alignment of the elastic and muscular elements of the media. Upstream to the region of constriction the media had a well-developed muscularis and elastica. Beyond the constricting diaphragm the arterial wall was considerably thinned and the muscularis and elastica were of lesser thickness. A specimen demonstrating these differences in thickness of the vessel wall as well as showing a valve-like structure is illustrated in fig. 6.

A thick-walled chick aorta above the region of narrowing, with reorganization of the elastic components of the media, and cystic change, is shown in figure 7.

In 5 of 8 dogs in which a subclavian artery had been partially constricted by the method described for chicks, a marked narrowing was present at the site of suture placement. A diaphragm occluded the lumen except for a small orifice which remained in all specimens. Histologic examination revealed a pattern of intimal ingrowth into the vessel, generally similar to that described above for the chick.

Growth around a Linen Suture. In 6 chicks a linen suture was pulled through the aortic lumen, leaving a "violin string" bridge across it. The linen became completely covered by intima. The upstream face of the suture was covered by a thin layer of endothelial cells and a small amount of subendothelial connective tissue. By contrast, the downstream face of the suture was covered by a relatively thick layer of connective tissue, sometimes with frond-like trailers (fig. 8).

Blood Pressures. Evidence for dynamic effects of the narrowing was seen in blood pressure measurements. The intraarterial blood pressure above and below the constriction was measured with a Sanborn electromanometer in 19 chicks. The arterial pressure above the stenosis was significantly higher than the usual levels for chicks of comparable age in 4 of the test animals. The blood pressure below the site of constriction was markedly reduced. A marked pressure drop across the constriction was observed in 7 of 8 chicks in which pressures above and below the constriction were measured simultaneously.

DISCUSSION

The present experiments demonstrate that partial narrowing of the lumen of a blood vessel may be followed by an ingrowth of connective tissue and the development of a

FIG. 7. A cross section of an aorta immediately above a region of narrowing as in figure 6. A fibrous ingrowth into the lumen is seen at 6 to 8 o'clock. Beneath the plaque cystic spaces are seen between the lines of elastic fibers. Marked differences in the thickness and development of the media may be noted between thick wall on the right and the thinner wall at 10 o'clock. Hematoxylin and eosin. × 10.

progressive stenosis. The ingrowth resembles that at sites of valvular stenoses, in coarctation of the aorta, as well as that of the postnatal stenotic process in the ductus arteriosus.

The progression of these experimental lesions recalls the well-established principle that after initiation, as in an episode of rheumatic fever, stenotic lesions are often progressive. Such progression of stenosis ordinarily is not a continuous process. Instead, clinical evidence suggests that the progression is accelerated at times of disturbances of the connective tissues, as during a recurrence of rheumatic fever. No evidence for regression of such stenotic lesions has been indicated on the basis of clinical or pathologic findings.

An insight into the possible mechanism of such progressive stenotic lesions may be derived from hydraulic considerations. It is well appreciated that the fibers of bones, tendons, muscles and other collagenous tissues align themselves along lines of stress.[10, 11] The structure of blood vessels, derived from similar anlage[9] may similarly be determined by mechanical factors (fig. 9).

Intima. The normal intima of blood vessels is ordinarily very thin, consisting primarily of flattened endothelial cells and a thin subendothelial layer. It is suggested that the flattening of the endothelial cells and their functional specialization may result from their continuous compression by the lateral blood pressure.

The endothelium, like other connective tissue, has a great potential for growth.[12] Ordinarily this potential becomes apparent only after injury to the vessel wall,[13, 14] when the endothelial cells proliferate rapidly and reline the injured area. This growth potential can also manifest itself in the proliferation of the intimal cells into the lumen, with an ultimate complete obstruction to flow. Such a sequence occurs when blood is stripped from a segment of artery that is then tied at both ends. A rich intimal proliferation of young connective tissue quickly fills the lumen under these circumstances.[15] It is here suggested that this potential growth is usually inhibited by the distending pressure normally present in arteries and veins, presumably by a process akin to *pressure atrophy.*

In the present experiments, narrowing of the vessel lumen by placement of a tuck probably increased the velocity of the bloodstream at this site. A marked pressure drop would result locally, in accord with the principle of conservation of energy (Bernoulli*). As the velocity increases to a critical value the distending pressure may fall to or even below the level of the surrounding tissue pressure. The normal distending pressures are thus eliminated and the intimal layer, freed from the atrophic influences of pressure, can grow into the lumen.

As growth proceeds the narrowing of the lumen becomes more severe; the velocity of the stream is further increased and the distending pressure at the site falls still more. Stenosis thereby tends to become progressive.

*The total energy at any point in a stream is equal to that expended as lateral or distending pressure, plus that expended as velocity. An increase in velocity at a site will therefore necessarily result in a local fall in the distending pressure.

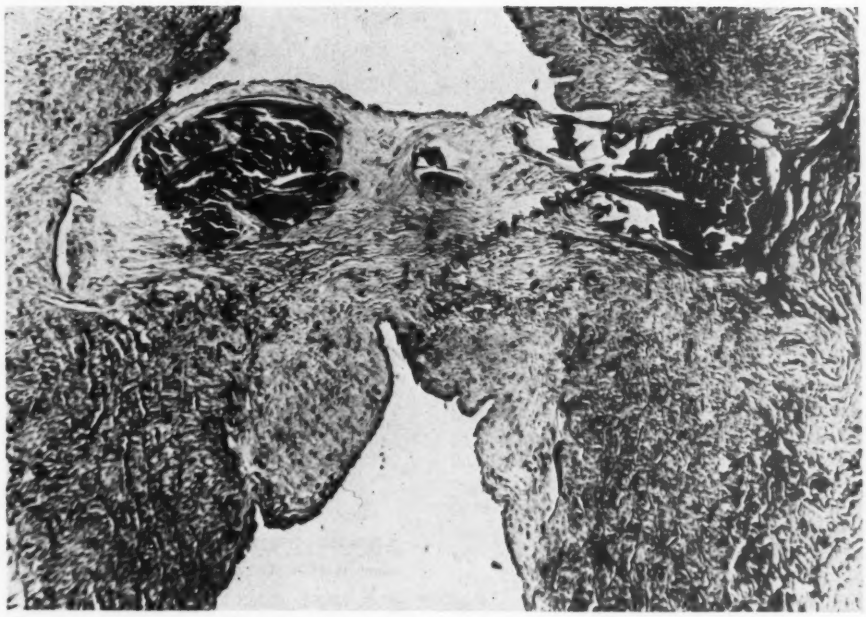

FIG. 8. A section of chick aorta with a linen ligature placed across the lumen 3 months previously. Top is cardiad. The linen fibers are seen as dark-staining bundles at left, center, and right. A thin intimal growth covers the cardiad (upper) face of the thread. The peripheral face of the thread is covered by a thick growth that takes the form of thick papillae.

This interpretation provides an explanation for the paradox that the high upsteam pressure never dilates and "cures" a stenotic vascular ring. Similarly, restenosis of a surgically dilated mitral ring[16] might be expected when a high velocity flow through it persists because of inadequate dilatation or because of the generation of an insufficiency at the site.

This hypothesis is supported by the experiments in which a suture bridging the lumen became covered by endothelium and connective tissue. The thinly covered upstream side was constantly subjected to the pressure of the stream, presumably inhibiting proliferation at this site. The downstream side of the suture was thickly covered with connective tissue and endothelium; it is this portion that would have the lowest pressures acting on it. The distribution of growth along the suture therefore conforms with growth patterns expected on the basis of the hydrodynamic interpretation given above.

In other studies we have illustrated some of these streamline patterns by use of "wall-mapping" technics demonstrating the development of valves and stenoses of similar appearance.[7]

Further support for the hydraulic concept may be derived from unpublished data in cholesterol-fed chicks that show fatty infiltrations of the arterial wall above and below the site of narrowing, but not at the constriction itself. The high velocity at the narrowing results in a low local pressure, which would be associated with a reduced infiltration at this site.

Orifice. The process of progressive stenosis reaches an ultimate end point, at which a small probe patency remains. As the lumen becomes progressively narrowed, the resistance to flow through it rises sharply (Poiseuille's law) and the velocity is reduced. The resulting local increase in lateral pressure may then act to halt intimal ingrowth. An equilibrium is thus achieved between lumen

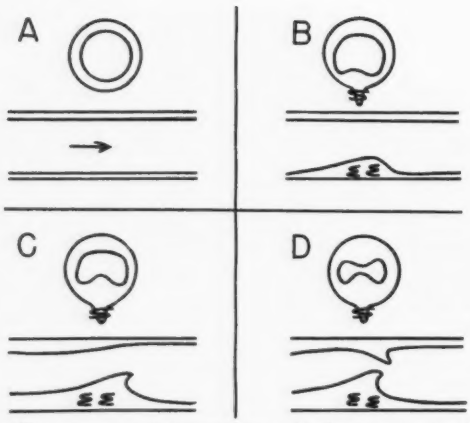

FIG. 9. An interpretation of the sequence of events after placement of a tuck in a blood vessel. In *A*, radial and longitudinal section of the vessel are shown, the arrow giving the direction of flow. In *B*, sutures (*s*) are placed in an arc of the vessel wall, reducing the lumen. In *C*, ingrowth into the lumen is indicated in the region near the sutures. In *D*, concentric intimal ingrowth narrows the lumen producing a coaretation-like obstruction. Thickening of the wall above and thinning of the wall beyond the narrowing are related to the pressures present in the various portions of the vessel.

size and velocity, resulting in the maintenance of anatomic but "nonfunctional" patency. Probe patency of this type is common in stenotic processes such as in coaretation of the aorta, as well as in patent foramen ovale and ductus arteriosus without significant shunts.[17, 18]

Media. The response of the media is determined primarily by the *tension* on the blood vessel wall. If either the pressure or the diameter is increased, the tension is increased proportionately.[19] The medial elements then increase in amount and become compact. At sites of reduced pressure these elements of the media are diminished. The same mechanisms may account for the pattern of medial development in our specimens in the segments of the arteries where the pressure was normal or raised. Above the stenotic site, the medial wall was markedly thickened. Beyond the site of constriction, where the arterial pressure was diminished, the elastic elements of the vessel were reduced and the wall was notably thinned. These findings accord with the concept that the degree of development of the media is an adaptive response to the distending force it must meet. Such a concept would explain the medial thinning at atheromatous plaques,[20] since the "lift" of the bloodsteam would actually reduce the tension acting on the media under the plaque. A "lifting" force of this type may also account for the presence of "cystic" spaces in the media at a site of partial obstruction (fig. 7).[21, 22]

These studies suggest that the structure of blood vessels may depend to a significant extent upon the action of physical forces on the intimal and medial elements of the vessel wall.

SUMMARY

The lumen in blood vessels of chicks and dogs was reduced by placing a mattress suture in an arc of the wall. A small reduction in the cross section area produced a localized inflammatory response; at autopsy the cross section was of the preoperative size. Placement of the suture to produce a marked reduction in cross section area was followed by intimal proliferation at the site, with the development of valve-like or progressive, coaretation-like stenoses. The intimal proliferation appears to result from hydrodynamic factors lowering the pressure locally.

The medial changes were related to the tension acting on the vessel wall. Above the constriction, where the pressure was high, the media tended to be thickened. Medial cystic spaces were present near the constriction. At the constriction, the lines of the elastic fibers were reorganized in patterns that may relate to the stress forces in this region. Below the narrowing, the medial wall was thin.

ACKNOWLEDGMENT

I am indebted to Chizuko Kakita, B.S., Christine B. Williams, B.A., and Walter Stone, M.D., for assistance in the surgical preparations; and to Francis Williams, M.A., for the blood pressure determinations. T. T. Bronk, M.D., of the Department of Pathology gave assistance in the description of the microscopic specimens. Dr. L. N. Katz, Director of the Cardiovascular Department, Michael Reese Hospital, contributed to many discussions during the development of the study.

SUMMARIO IN INTERLINGUA

Le lumine de vasos de sanguine de gallinas e canes esseva reducite per effectuar un sutura de matrassero in un arco parietal. Un micre reduction in le area del section transverse produceva un responsa de inflammation localisate. Al necropsia le section transverse habeva le magnitude preoperatori. Quando le sutura esseva placiate de maniera que un marcate reduction esseva effectuate in le area del section transverse, le consequentia esseva un proliferation intimal al sito del operation con le disveloppamento de stenoses progressive de character coarctatori e valvuloide. Il pare que le proliferation intimal resulta de factores hydrodynamic que effectua un reduction local del pression.

Le alterations medical esseva relationate al tension que ageva super le pariete del vaso. Supra le constriction, ubi le pression esseva alte, le media exhibiva le tendentia de spissificar se. Cystic spatios medial esseva presente in le vicinitate del constriction. Al sito del constriction, le lineas del fibras elastic esseva reorganisate in configurationes que es possibilemente relationate al fortias de tension in iste region. Infra le constriction le pariete medial esseva tenue.

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Bronchial Obstruction Due to Pulmonary Artery Anomalies

I. Vascular Sling

By Stephen Contro, M.D., Robert A. Miller, M.D., Harvey White, M.D., and Willis J. Potts, M.D.

A left pulmonary artery, coursing anomalously above the right bronchus and behind the trachea en route to the left lung, can produce disabling respiratory symptoms. Three cases observed by the authors are presented in detail and 5 similar cases, previously reported, are reviewed. The clinical features are those of tracheobronchial obstruction, occurring early in life, associated with endoscopic evidence of extrinsic pressure on the right bronchus and posterior wall of the trachea. The importance of the clinical recognition of this anomaly is stressed, since it appears to be amenable to surgical correction.

RECENT advances in surgical technics have renewed interest in cardiovascular malformations that cause bronchial or esophageal obstruction. Most of this recent work has been concerned with a variety of anomalies produced by a deranged development of the 6 primitive aortic arches. These include double aortic arch, right aortic arch with ductus or ligamentum arteriosum, and anomalous subclavian or carotid arteries. However, the occurrence of pulmonary artery anomalies as a cause of bronchial obstruction has remained almost wholly unrecognized. In a recent publication one of the authors reported a case in which an anomalous left pulmonary artery embraced the right main bronchus and the lower trachea so tightly that it produced marked narrowing of the airways.[1] Two additional patients have since been observed and with the earlier case form the substance of this report.

Case Reports

Case 1. K. B., a white baby girl was seen at Children's Memorial Hospital at the age of 2½ months, because of spells of dyspnea and cyanosis. She was born at full term of an uncomplicated pregnancy. No abnormality was noted at birth nor during the first month of life. Then she began to have brief episodes of dyspnea and cyanosis, especially after crying. She received x-ray therapy to the anterior chest wall after a roentgenogram of the chest was interpreted as revealing an enlarged thymus gland. Her respiratory symptoms increased both in frequency and severity and were associated with periods of unconsciousness. On admission she appeared moderately dyspneic, but not cyanotic at rest. The suprasternal notch retracted with each inspiration and an inspiratory and expiratory wheeze was present.

Chest films (fig. 1) showed narrowing of the lower part of the trachea and a left apical density, interpreted as a thymic shadow; a marked indentation of the anterior wall of the esophagus was seen just below the aortic arch with no posterior displacement (fig. 2). An electrocardiogram and other laboratory tests were within normal limits.

The diagnosis of a vascular anomaly, causing tracheoesophageal compression was considered, and, because of the severity of symptoms and unfavorable prognosis, surgery was undertaken. After a left thoracotomy, cause of extrinsic tracheal compression was not found. With the chest open, bronchoscopy revealed moderate stenosis of the trachea at the level of the carina, involving as well the opening of the left main bronchus. The right main stem bronchus was almost completely collapsed. The bronchoscope could be passed easily into the lumen of the right bronchus, but upon withdrawal of the instrument compression recurred. A dilator was repeatedly passed through the narrowed area without relief of the obstruction. At this point it was deemed that no further surgery could be performed and the chest was closed. The patient's respiratory symptoms grew worse immediately and death occurred in 3 days.

Postmortem examination revealed tracheal stenosis at the carina, partially involving the opening of the left main stem bronchus; ulcerative

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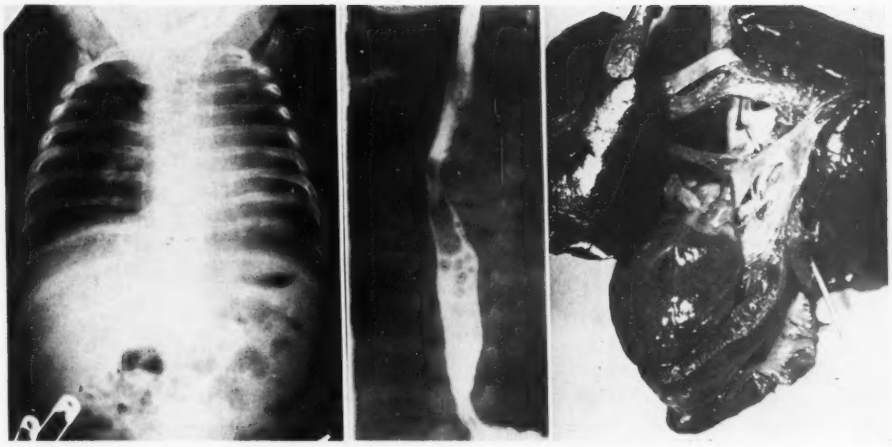

FIG. 1 *Left.* Case 1. Chest film in the frontal projection showing increased density of left upper lung field (lateral projection, which showed a distinct narrowing of the lower portion of the trachea did not lend itself to satisfactory reproduction).

FIG. 2 *Middle.* Case 1. Barium swallow showing extrinsic pressure defect on the anterior wall of the esophagus at about the level of the carina. Note also the congenital deformity of the upper dorsal spine (hemivertebrae).

FIG. 3 *Right.* Case 1. Posterior view of the mediastinal structures with probe at site of bifurcation of main pulmonary artery into left pulmonary artery and right pulmonary artery with its apical branch.

bronchitis; resorption atelectasis of the left lung; and an anomalous left pulmonary artery. While the right pulmonary artery coursed in a normal direction to the right hilum, the left pulmonary artery crossed anterior to the right main bronchus and encircled the trachea, compressing both structures (fig. 3). It then coursed posteriorly between the trachea and esophagus to emerge on the left side, just superior and posterior to the left main stem bronchus and then entered the left lung.

Case 2. C. D., a white baby boy, the product of a full-term pregnancy and uneventful delivery, was first admitted to Children's Memorial Hospital at the age of 9 days because of episodes of dyspnea and cyanosis. These were noticed immediately after birth, were associated with inspiratory retractions, and bore no relation to feeding. Pertinent physical findings on admission consisted of sternal retractions with each breath, audible prolonged expiratory wheeze, decreased breath sounds over the right chest, and displacement of the cardiac dullness to the left.

X-rays (fig. 4) showed marked emphysema of the right lung with displacement of the mediastinal structures to the left; the mediastinum shifted with each expiration; and an esophogram was normal. Bronchoscopy revealed a normal patent larynx with tracheal deviation to the left. The carina was sharp and the left main bronchus was normal, but the right main bronchus immediately above the upper lobe orifice and the lower trachea was compressed to a small slit by pressure on the lateral wall. The bronchoscope was passed into the bronchus without appreciable resistance, but compression recurred when the instrument was removed. Bronchography (fig. 5) also indicated external pressure on the right main stem bronchus and lower trachea. Laboratory tests including an electrocardiogram were within normal limits.

The hospital course was marked by gradual improvement in the respiratory symptoms, so the child was sent home. He took his feedings well, gained weight, and generally did well for approximately 2 months. Then, spells of cyanosis and dyspnea reappeared with increasing frequency associated with a constant expiratory wheeze. Surgery was then considered imperative.

The right hilus, right bronchus, and lower segment of the trachea were adequately exposed through a right thoracotomy. The main pulmonary artery coursed directly toward the right side and divided into its 2 main branches over the hilum of the lung. While the right pulmonary artery went directly to the right lung along normal pathways, the left pulmonary artery circled anteriorly around the right bronchus and lower part of the trachea and then coursed posteriorly and to the left, behind the trachea and in front

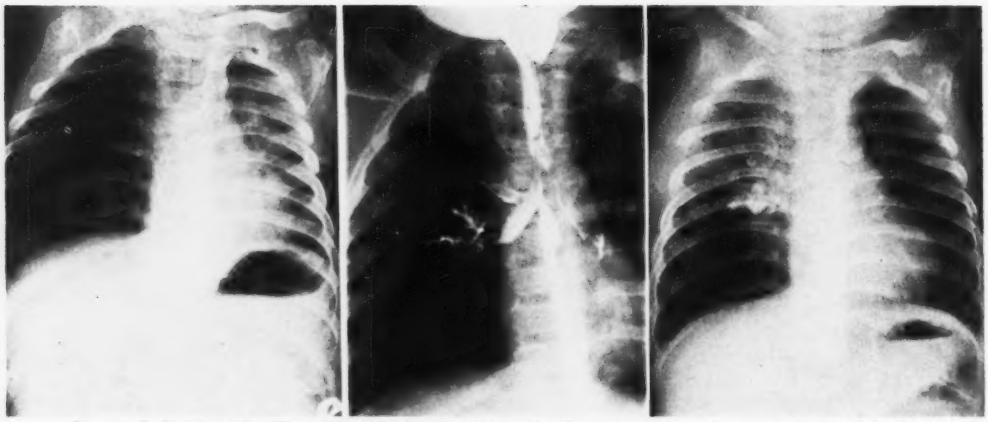

FIG. 4 *Left.* Case 2. Chest film in the frontal projection showing emphysema of the right lung with mediastinal displacement to the left.

FIG. 5 *Middle.* Case 2. Bronchogram showing extrinsic pressure defect on the lower trachea and proximal part of the right main bronchus above the upper lobe orifice.

FIG. 6 *Right.* Case 2. Chest film obtained on the eleventh postoperative day showing equal expansion of both lungs with heart in normal position.

of the esophagus and aorta. The right bronchus was reported to be paper thin and transparent at the point of pressure by the artery. The left pulmonary artery was divided at its origin. The distal segment was then moved medial to the right bronchus and trachea and an end-to-end anastomosis was hurriedly performed with the proximal end.

The postoperative course was uneventful with the exception of a tracheobronchitis of short duration. Respiratory symptoms and obstructive emphysema of the right lung disappeared. An x-ray (fig. 6) on the eleventh postoperative day showed equal expansion of the lungs and the heart in normal position. During the ensuing months, the patient suffered occasional attacks of mild stridor, which later disappeared.

Case 3. J. E. S., the fourth child of a healthy mother was admitted to Children's Memorial Hospital at 15 hours of age because of imperforate anus, cleft lip and palate, and possible congenital heart disease. The infant had been delivered without difficulty and had required no oxygen. Physical examination on admission revealed a well nourished 6-pound white male in good general condition. There was an imperforate anus and a rather severe cleft lip and palate. There was no cyanosis at rest and no cardiac murmur was heard. The heart tones were normal and the femoral arteries were palpable.

X-ray of the chest revealed normal heart and lungs. The hemoglobin was 20.5 Gm. per cent, the white blood cell count was 32,000/mm.^{3}, and the urine was normal. The electrocardiogram suggested right heart strain.

At 48 hours of age a primary anorectal anastomosis was done under general anesthesia. The immediate postoperative course was uneventful. About 48 hours after surgery the child had a sudden severe episode of dyspnea, accompanied by gray pallor and cyanosis. The respirations became erratic and the infant died shortly thereafter.

Pertinent postmortem findings were imperforate anus, surgically repaired; cleft lip and palate; persistent left superior vena cava draining into the coronary sinus; common ventricle and atrioventricular orifice with 5 valves; dextroposed aorta arising slightly anterior to the pulmonary artery; pulmonary artery originating to the left of the aorta. At a distance of 0.5 cm. from the valve ring the pulmonary artery curved sharply to the right, crossing the midline. As it passed over the right bronchus it divided, one branch going directly to the right lung. The other branch coursed around the trachea near its bifurcation, passed anterior to the esophagus and parallel to the left main bronchus into the left chest and entered the parenchyma of the left lung after dividing into 3 branches.

DISCUSSION

The soft nature of the tracheobronchial cartilages in infancy explains the ease with which extrinsic structures can compress the major airways. Cardiovascular anomalies occupy a prominent place in the etiology of tracheobronchial compression. Although the markedly enlarged heart can produce com-

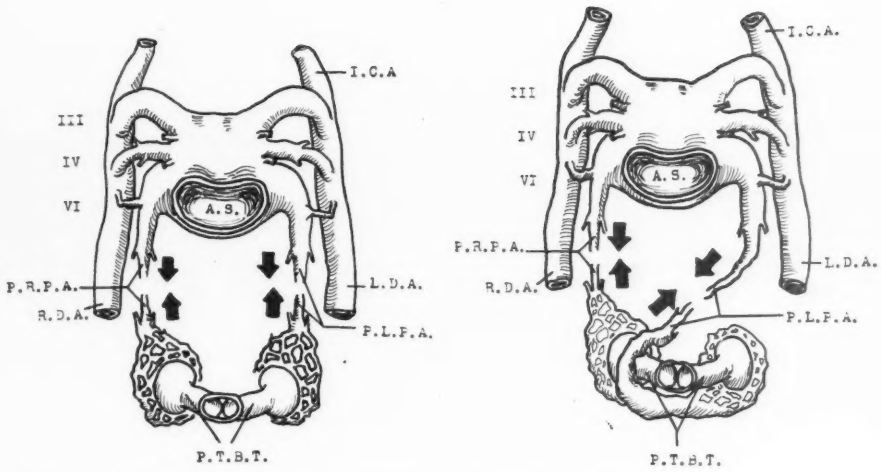

FIG. 7. Diagrams illustrating the development of the primitive pulmonary arteries in normal embryo (*Left*) and in the malformation under discussion (*Right*). *A.S.*: aortic sac; *I.C.A.*: internal carotid artery; *L.D.A.*: left descending aorta; *R.D.A.*: right descending aorta; *P.R.P.A.*: primitive right pulmonary artery; *P.L.P.A.*: primitive left pulmonary artery; *P.T.B.T.*: primitive tracheobronchial tree; *III*, *IV*, *VI*: third, fourth, sixth aortic arch.

pression of the bronchial tree,[2] vascular anomalies are more important in the genesis of respiratory tract obstruction. In 1837 Von Siebold[3] first reported a case in which death due to respiratory distress was caused by a double aortic arch. Thenceforth, several similar cases have been reported and much stress has been laid on the common syndrome produced by double aortic arch and constricting ring formed by a right aortic arch with persistent ligamentum arteriosum or anomalous left subclavian artery. The successful surgical treatment of double aortic arch, first reported by Gross[4] in 1945, stimulated new interest in the study of these conditions. Despite the wealth of literature accumulated on this subject, only very rare references are found pertaining to pulmonary artery anomalies, as a cause of respiratory obstruction.

The 3 cases herein reported are strikingly similar and represent instances of a "vascular sling"* formed by an aberrant left pulmonary artery that encircled the right main stem bronchus and the trachea. As a consequence the right bronchus and posterior wall of the trachea were compressed, causing respiratory embarrassment. A thorough search of the literature revealed 5 similar cases.[5-8] The clinical features of this anomaly consist of symptoms and signs of tracheobronchial obstruction, occurring shortly after birth. Although other malformations (such as double aortic arch and related developmental anomalies of the fourth aortic arch, tracheomalacia, tracheal stenosis, tracheal web, tracheo-esophageal fistula, etc.,) can result in similar respiratory derangement, the radiologic and endoscopic findings are sufficiently distinctive in most of the cases to permit a correct diagnosis. While bronchoscopic examination indicates the presence of extrinsic compression on the right bronchus and lower trachea, the esophogram does not show a posterior indentation and thus excludes a true vascular ring. Compression of the anterior wall of the esophagus, as noted in case 1 and in the first case reported by Wittenborg et al.,[8] further suggests that the cause of obstruction must lie anterior to the

*In reference to this type of anomaly, the term "vascular sling" rather than "vascular ring" should be adopted to avoid confusion with more common systemic arterial malformations causing constriction of the trachea and esophagus.

esophagus. Obstructive emphysema of the right lung, as noted in case 2 and in the case reported by Morse and Gladding,[7] lends additional support to the diagnosis of this malformation.

The embryologic origin of such a vascular anomaly is of some interest. Early in embryonal life (4 mm. to 40 mm. of embryonic length) each pulmonary artery, forming from the primitive pulmonary arteries and elements of the sixth arch, seeks a vascular channel in the mesenchyme, surrounding the newly sprouted lung bud (fig. 7*A*). Normally, the left pulmonary artery finds its connection in the hilar area of the left lung bud and, as the bronchial tree progresses in its development, the usual relationship of the left pulmonary artery to the left bronchus results. If, however, the timing is upset during the formation of these structures, an anomaly may result. For example, if the growth of the left pulmonary artery is delayed or that of the primitive left lung bud is accelerated, they cannot meet normally. The normal path of the left pulmonary artery to the left lung bud would be obstructed, so to speak, by the overgrown left primitive bronchus. In order to establish its mesenchymal connection, the primitive left pulmonary artery now would have to pass anterior to the right bronchus, posterior to the trachea, then to the left into the tissue surrounding the left lung bud (fig. 7*B*). Similar embryologic speculation on the origin of this anomaly is offered by Scheid.[5]

It appears that major developmental anomalies are often associated with the "vascular sling" formed by an aberrant left pulmonary artery. They may dominate the clinical picture. However, the occurrence of this lesion as an isolated anomaly, which is surgically correctible, seems to be almost as frequent (our case 2, Morse's case,[7] and Welsh's case[6]). Therefore the clinical recognition of this condition is not only of academic interest but also of practical concern.

Whenever suspicion arises of an anomalous left pulmonary artery, thoracotomy should be performed on the right side.

Summary

Three patients are reported in whom the left pulmonary artery coursed anomalously anterior to the right bronchus and behind the trachea with consequent compression of these structures. A review of the literature revealed 5 similar case reports. The clinical picture associated with this congenital lesion is dominated by symptoms and findings of bronchial obstruction, when not obscured by other major associated anomalies. Bronchoscopic findings indicative of extrinsic pressure and the absence of indentation of the posterior wall of the esophagus assist in the delineation of this lesion. Because this anomaly is surgically correctible, importance of its clinical recognition is stressed.

Summario in Interlingua

Es reportate le casos de tres patientes in qui le arteria sinistro-pulmonar sequeva un anormal curso anterior al broncho dextere e in retro del trache, con le effecto de compression del mentionate structuras. Un revista del litteratura revelava reportos de 5 simile casos. Le tableau clinic associate con iste congenite lesion es dominate per symptomas e constatationes de obstruction bronchial, providite que illos non es celate per altere major anomalias associate. Constatationes bronchoscopic que indica le presentia de un pression extrinsec e le absentia de indentation del pariete posterior del esophago es de adjuta in le delineation de iste lesion. Proque le anomalia pote esser corrigite per medios chirurgic, le importantia de su recognition clinic es sublineate.

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Bronchial Obstruction Due to Pulmonary Artery Anomalies

II. Pulmonary Artery Aneurysm

By Stephen Contro, M.D., Robert A. Miller, M.D., Harvey White, M.D., and Willis J. Potts, M.D.

In a previous publication attention was drawn to the occurrence of pulmonary artery anomalies as conditions causing tracheobronchial obstruction. In the present report 2 infants are presented in whom a large aneurysm of the pulmonary artery pressed upon the walls of the left bronchus, producing severe respiratory symptoms.

DURING the past decade vascular malformations of the superior mediastinum have been the object of intense clinical interest. However, the occurrence of anomalies of the pulmonary artery as a cause of tracheobronchial obstruction has gone almost unrecognized. We previously reported 3 cases in which significant respiratory obstruction was produced by a left pulmonary artery coursing anomalously above the right bronchus and behind the trachea, thus producing a "vascular sling."[1]

The present report is concerned with the description of 2 patients in whom disabling respiratory difficulties resulted from pressure on the left bronchus by a large pulmonary artery aneurysm, a hitherto undescribed condition.

Case Reports

Case 1. D. M., a 3-month-old white boy was admitted to Children's Memorial Hospital because of "congenital heart disease and dextrocardia." He was the product of an uneventful gestation and delivery. At birth an imperforate anus was found with a tiny fistulous tract, terminating just lateral to the median raphe. This was repaired and subsequently dilated with satisfactory resumption of bowel function. Cyanosis, especially on crying, rapid and labored respirations, and a systolic murmur were noted shortly after birth.

On admission the infant appeared well nourished with mild cyanosis of the lips and extremities. The heart tones were best heard over the right chest and the cardiac impulse was palpable in the right anterior axillary line. A rather harsh systolic murmur was heard over the entire chest. In the second and third left intercostal space was a loud to-and-fro murmur. The left chest was hyperresonant and rales were heard at the left base. The liver edge was felt 1 inch below the right costal margin. The electrocardiogram revealed upright P waves in the standard limb leads with shift of the transition zone to the right in the chest leads. Roentgenogram (fig. 1) and fluoroscopy of the chest showed a marked emphysema of the left lung with shift to the right of the heart and mediastinal structures. In addition, a large pulsating mass was present in the region of the pulmonary artery segment. A venous angiocardiogram revealed opacification of the left atrium from

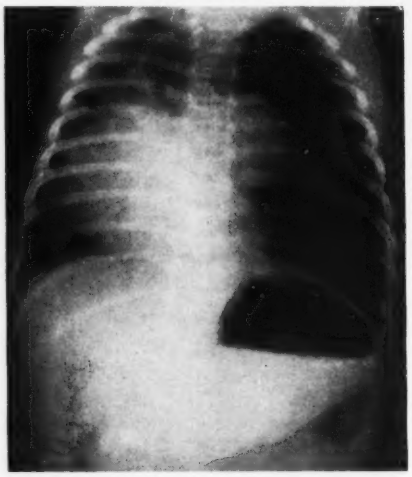

Fig. 1. Case 1. Roentgenogram in the frontal projection showing marked emphysema of the left lung with displacement of the heart and mediastinum to the right and a large mass in the region of the left pulmonary artery.

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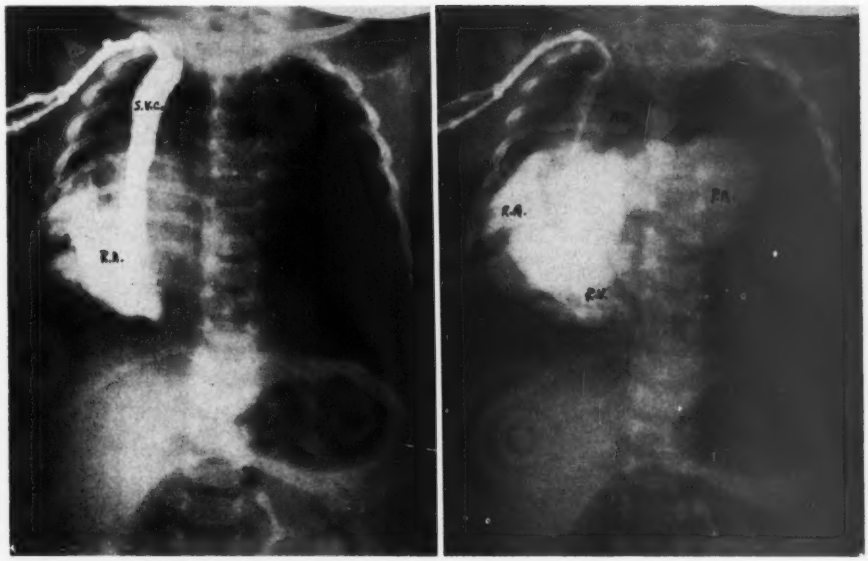

FIG. 2. Case 1. *Left.* Angiocardiogram showing the contrast medium filling the superior vena cava and right atrium. *Right.* Later in the cycle there is opacification of the right ventricle and of a markedly dilated main and left pulmonary artery. The aorta appears to fill directly from the right ventricle.

the right atrium and of the aorta from the right ventricle, and the presence of a huge aneurysm of the pulmonary artery (fig. 2).

Because of the severity of the respiratory symptoms, surgical relief was attempted. Through a left thoracotomy a huge aneurysmal dilatation of the left pulmonary artery and similar but less pronounced changes of the right pulmonary artery were found. The left bronchus was collapsed and remained so when the aneurysmal left pulmonary artery was elevated. Although it was realized that pneumonectomy in this age group is almost uniformly fatal, it was thought that the severe mediastinal shift could be corrected in no other way. The left pulmonary artery was ligated and the emphysematous left lung was removed. The infant died 10 hours later.

At autopsy a tetralogy of Fallot with a widely patent foramen ovale was found. The main pulmonary artery measured 1.5 cm. in diameter at its origin from the right ventricle; the left pulmonary artery, which was removed at surgery, 3 cm. at about 0.5 cm. from the bifurcation; the right pulmonary artery was also dilated and became bulbous at the right hilum.

Case 2. I. T., a white baby girl, born at full term of an uncomplicated pregnancy, was seen at the Children's Memorial Hospital at the age of 13 days because of rapid shallow respirations and cyanosis of the lips and fingernails. On admission the infant appeared well nourished, tachypneic, with minimal retractions of the suprasternal notch and mild cyanosis. The heart tones were best heard over the right precordium and the point of maximal pulsation was felt in the fourth right intercostal space and nipple line. A loud to-and-fro murmur with a continuous thrill was present over the second and third left intercostal space parasternally. The lungs were clear. The liver edge was felt just below the right costal margin. Roentgenogram (fig. 3) and fluoroscopy of the chest showed the heart and mediastinal structures markedly shifted to the right with a large pulsating density at the level of the pulmonary artery segment. The left lung was emphysematous. A venous angiocardiogram (fig. 4) revealed a huge aneurysmal dilatation of the main and left pulmonary artery with no definite evidence of shunt in either direction.

The infant's hospital course was marked by recurring episodes of dyspnea and cyanosis. Death occurred during one such attack.

Postmortem examination revealed tetralogy of Fallot, aneurysm of the main and left pulmonary arteries, and obstructive emphysema of the left lung.

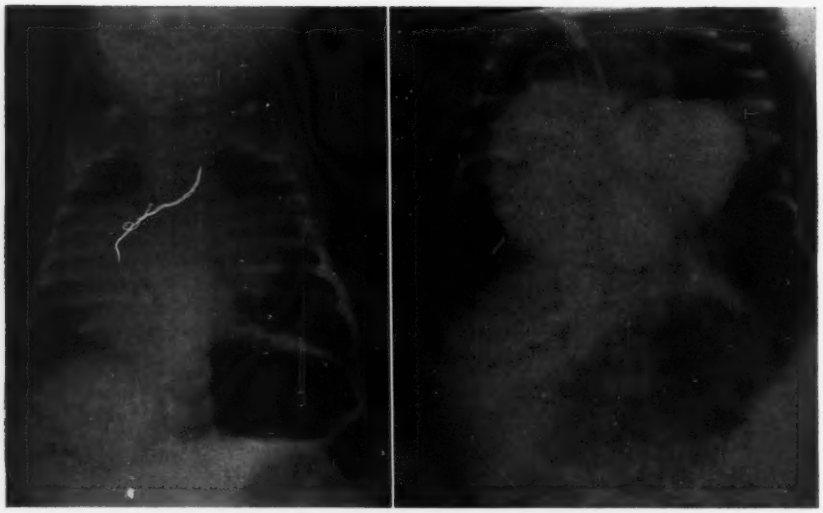

FIG. 3 *Left.* Case 2. Roentgenogram in the frontal projection showing emphysema of the left lung, shift of the heart and mediastinal structures to the right, and a large round density in the region of the pulmonary artery segment.

FIG. 4 *Right.* Case 2. Film obtained late in the cycle with contrast material outlining the right and left cardiac chambers, and a hugely dilated main and left pulmonary artery. Aortic filling followed opacification of the left chambers.

DISCUSSION

Aneurysm of the pulmonary artery is one of the rare lesions of the cardiovascular system, occurring at a rate of approximately 1 in 14,000 autopsies.[2] Exceedingly uncommon are those forms of congenital aneurysm that cannot be accounted for by any known cause of pulmonary artery dilatation, viz., atrial septal defect, ventricular septal defect, patent ductus arteriosum, valvular pulmonic stenosis, and primary pulmonary hypertension.

The symptoms and findings of this lesion were comprehensively reviewed by Boyd and McGavack[3] and by Deterling and Clagett.[2] These include dyspnea, cough, chest pain, hemoptysis, and hilar mass with expansile pulsations. However, a thorough search of the literature failed to reveal any case in which a pulmonary artery aneurysm encroached upon the bronchial tree, producing serious obstructive symptoms.

The 2 cases herein presented are strikingly similar. In both a huge aneurysmal dilatation of the pulmonary artery impinged upon the walls of the left bronchus, leading to obstructive emphysema of the left lung and mediastinal displacement to the right. Unlike other forms of tracheobronchial obstruction of vascular nature, this lesion does not appear to be surgically correctible inasmuch as irreversible changes of the bronchial walls necessitate pneumonectomy, which is usually fatal in the first few months of life.

SUMMARY

Two infants with severe respiratory embarrassment secondary to compression of the left bronchus by a large aneurysmal dilatation of the pulmonary artery are presented. Review of the literature failed to reveal any similar case.

SUMMARIO IN INTERLINGUA

Es presentate le casos de duo infantes con sever embarrasso respiratori secundari a com-

pression del broncho sinistre per un grande dilatation aneurysmic del arteria pulmonar. Le revista del litteratura non produceva ulle simile caso.

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A simple safe test for the detection of atrial septal defects which is of value in the symptomless patient is described. This test is based upon the rise in the right atrial pressure above the resting level that occurs immediately after performance of the Valsalva maneuver. With an atrial septal defect or a patent foramen ovale the sudden rise in net right atrial pressure during the first few seconds after the end of the Valsalva maneuver causes a right-to-left pressure gradient across the defect with desaturated blood going into the left atrium. The resulting change in arterial oxygen saturation may be detected by the ear oxymeter method. In 32 patients with suspected atrial septal defects study by means of this test proved to be of value. In 12 in whom the diagnosis was proved by cardiac catheterization or thoracotomy, characteristic and reproducible changes in arterial oxygen saturation were found. In 14 further patients with positive oxymeter responses to the Valsalva test, there was catheter evidence of a left-to-right shunt at the atrial level but definite anatomic proof of an atrial septal defect was lacking. Five patients had a negative response. Three subsequently were found not to have atrial septal defects and 2 had congestive cardiac failure associated with atrial septal defects. In these latter 2 patients, Muller's maneuver or elevation of the legs caused a fall in systemic arterial oxygen saturation, enabling the correct diagnosis to be made.

Sagall

SPECIAL ARTICLE

William Harvey Speaks

By EDGAR V. ALLEN, M.D.

. . . If you do remember,
I send it through the rivers of your blood,
Even to the court, the heart, to the seat o' the brain:
And through the cranks and offices of man,
The strongest nerves and small inferior veins
From me receive that natural competency
Whereby they live.
—Shakespeare: *Coriolanus*

THE Program Committee has asked me to open the General Sessions of this Annual Scientific Meeting of the American Heart Association by some remarks about William Harvey, to the memory of whom this program is dedicated. This I am happy to do, even though I am quite aware that much already has been written about this giant on the scene of clinical physiology. Thus it is that, at the risk of offending some, I have chosen to depart from the conventional in treating of this man whose work was so unconventional for his own times. To set the stage, I invite you to go back with me some 300 years in history.

The time is 1654. The place is London. The occasion is the meeting of the College of Physicians. England is in the Renaissance period, which in Europe began about a century earlier as a result of the studies of Copernicus, the Polish genius, who died in 1543, 35 years before the birth of Harvey. Copernicus did much to destroy the dark ages of the intellect, during which, as in centuries gone by, man clung to the benighted view that the whole universe had been made for man. Before Copernicus it was believed that the planets moving eastward most of the time, periodically slowed down until they actually came to a halt, and then reversed themselves to their original positions, only to resume their eastward journey a second time, and to repeat this cycle endlessly. Copernicus proved that the earth is not the center of the solar system, but only of the orbit of the moon, and that in fact all the planets revolve around the sun. In the Renaissance period in which Copernicus lived for a good part of his 70 years, Columbus discovered a new continent, Magellan circumnavigated the globe, Vasco da Gama made the first sea voyage to India, Martin Luther brought about the Protestant Reformation, Michelangelo created the new world of art, Paracelsus and Vesalius laid the groundwork for modern medicine, Leonardo da Vinci flourished as a painter, sculptor, engineer, architect, physicist, biologist and philosopher, and Copernicus gave the world a new system for the universe in his the *De Revolutionibus Orbium Coelestium* on which he toiled for 30 years. He, like Harvey, was a student at Padua, immortalized by William Shakespeare, a contemporary of Harvey, as "... fair Padua, nursery of arts."

In Harvey's time England's naval might became established by the defeat of the Spanish Armada, English explorers opened new lands, and Shakespeare, Donne, Spenser, Dryden, Milton, Jonson, and Bacon flourished in the literary world. Harvey lived in the era of Galileo, Kepler, and Descartes. This was the English Renaissance, and Harvey contributed greatly to it. Like Copernicus, he lifted the curtain of ignorance, prejudice, and darkness.

Read at the meeting of the American Heart Association, Chicago, Ill., October 25 to 28, 1957.

What kind of man was William Harvey? John Aubrey wrote: "He was not tall but of the lowest stature, round faced, olivaster complexion, little eie, round, very black, full of spirit; his haire, black as a raven, but quite white 20 years before he died—he was as all the rest of the brothers, very cholerique, and in his young days wore a dagger; but the Doctor would be too apt to draw out his dagger upon very slight occasion."

A portrait showed Harvey to have been an alert, angry, keen-eyed, dark-complexioned little man—perhaps of the type known to Sir Francis Drake as an "Italianate Englishman"—but this portrait was made at an earlier time.

Although his book, *De Motu Cordis*, and his teachings stirred much controversy (his name came to be as much execrated as praised), he declined to answer his detractors, except in one instance.

After 1645, when he was 68 years old, his life was one of seclusion, for it had been disrupted by the Civil War and he had lost most of his treasured possessions. He suffered from gout, which he treated by putting his feet in cold water and then warming them at the stove. In his later years he sat much in caves which he had made for meditation. He developed a few harmless eccentricities. It has been said that he certainly had high blood pressure in his last years.

Now, as the audience waits in true respect—for his teachings by this time have been quite generally accepted—let me tell you what manner of physical man is about to address his colleagues. He is, as I have said, short in stature; his white hair recedes from his forehead and falls to his shoulders. His complexion is the color of a piece of oak and there are patches of high color on his cheeks. His mustache and goatee are white; his temporal arteries are prominent. As he comes to the lectern, he probably limps, for he has been much troubled with gout, and gossip has it that he takes opium. He does not appear a very happy or satisfied man.

The address which I am about to give was not delivered by Harvey, and my words have been freely intermingled with those of Harvey. To my knowledge, it is entirely accurate. Except for the concluding sentence, the last paragraph was written by Sir William Osler. The events subsequent to Harvey's time indicate that men can see new vistas by standing on the shoulders of giants.

Ladies and Gentlemen: I present to you an amiably fraudulent but a plausible and very brief autobiographical speech by Dr. William Harvey.

My colleagues in the College of Physicians—I am greatly honored to have been elected President of the College of Physicians of which I have been a member for so many years. I am now in my 77th year and my life has nearly reached a full circle. I remember with such pleasure the Lumleian Lectures which I gave here in the distant past of 1616-1621, and I regret that, recently, I have not been more among you. I note the natural consequences of aging. I believe that I cannot justify your trust in me, that I am physically and mentally capable of undertaking the responsibilities of the office which you have so graciously bestowed upon me. I must therefore decline. I have asked the privilege of speaking to you once more. This will, almost certainly, be my last appearance before you. In this presentation I claim the privilege of the old in matters of reminiscence and of philosophic consideration.

I thank God for a full life and an exciting one. No life is entirely serene, nor would I have it so, but in general fate has dealt kindly with me. It grieves me that my wife, Elizabeth Browne Harvey, raised in the tradition of medicine as the daughter of the personal physician to Queen Elizabeth, cannot know the great honor which you have offered me. I have regret that I have been denied the pleasures and sorrows of fatherhood, but at my age it is easier to be philosophic about this matter than it was at an earlier time.

I am thankful and pleased at all the honors which I have received, but it seems to me that they exceed the reasons for them. My years as physician to St. Bartholomew's would have been pleasing to any man however critical he may have been, and no man could have been other than imbued with thanks and gratitude for the privilege of having been personal physician and friend to their Serene Highnesses, James and Charles, Monarchs of the British Isles. I wish to pay tribute to my brother Eliab who has always managed my financial affairs; but for his continuing attention, poverty might well have directed my life in quite a different direction. Time has softened

the shock of the actions of that unruly mob which broke into my lodging in 1642 and destroyed my scientific notes. Perhaps John Aubrey was correct when he quoted me as having said that 'Man is nothing more than a great mischievous baboon.' As I look back over the years I believe that much better is it oftentimes to grow wise at home and in private than by publishing what you have amassed with infinite labor, to stir up tempests that may rob you of peace and quiet for the rest of your days.

It has been said that my teachings have done for biology what Copernicus did in giving us understanding of the universe. Aubrey had a different opinion, for he wrote that he heard me say that after my book on the circulation of the blood came out my practise fell mightily and 'twas believed by the vulgar that I was a crackbrained and that all the physicians were against me. Of course, that was many years ago. I make no claims but rather am satisfied with your opinion and with the judgment of history, of which I now have no information.

For more than a thousand years before my life, physicians and medical schools practised and taught the anatomical and physiologic theories concerning the heart, arteries, veins, and blood handed down from the great Asiatic-Greek physician, Galen, in the second century; his writings were considered almost of divine origin. Galen knew that the arteries contained blood—not air as maintained by Erasistratus but he erroneously believed that the liver was the center of the blood system, that digested food was carried to the liver and there transformed into blood with 'natural spirits' added. According to Galen, blood moved backward and forward in the body, by way of both veins and arteries, like the slow ebb and flow of the tides. Arterial blood from one side of the heart mixed with venous blood from the other side of the heart through minute pores. Only a few years before my birth, Andreas Vesalius proved that the pores of Galen did not in fact exist, and that there was no direct connection between the right and left sides of the heart. At about the same time, Servetus, later burned at the stake by John Calvin, stated his belief that blood circulates through the lungs although he did not recognize the heart as a pumping organ. My own teacher Fabricius, to whom I owe so much, discovered the valves in the veins, he learned to dissect and experiment on various kinds of animals. My four years as a student at Padua—which I believe to have been the Alma Mater of the Renaissance and particularly the guidance of that inspiring and famous teacher, Fabricius—first aroused my interest in circulation of the blood.

It has been said that my manuscripts and lecture notes are an almost illegible mixture of Latin and English. My handwriting seems to have been no better than that of many of my colleagues. To the complaint that there are many typographical errors in *De Motu Cordis,* I can only reply that I am not a printer, although I admit my handwriting may have been a handicap to him. As early as 1616, I was convinced that the movement of the blood is constantly in a circle and is brought about by the beat of the heart. I have been asked on occasions why 12 years elapsed between my arrival at these conclusions and the publication of my *Exercitatio Anatomica de Motu Cordis et Sanguinis in Animalibus.* I was in no hurry, for the crowd of foolish scribblers is scarcely less than the swarm of flies in the height of summer, and threatens with their crude and flimsy productions to stifle us as with smoke. Moreover, my theory of general circulation of the blood was of so novel and unheard of character, that I not only feared injury to myself from the envy of a few, but I trembled lest I have mankind at large for my enemies, so much had wont and custom, that had become as another nature, and doctrine once sown and that has struck deep root and rested from antiquity, influenced all men.

It is obvious, however, that truth should be accepted regardless of its source and that truth is of more value than antiquity. I learned and taught anatomy, not from books but from dissections, not from the position of philosophers but from the fabric of nature.

It is now clear, I believe, that in an hour's time the heart, in some 4000 beats, pumps out far more blood than the total amount of blood in the body and that the blood could be furnished in no other way than by making a circuit and returning. Blood goes to the arteries from the left side of the heart and returns to the right side of the heart by way of the veins. I have remained puzzled about one thing. I have never succeeded in tracing any connection between the arteries and veins by a direct anastomosis of their orifices, although I am convinced there must be such channels. I predict that, soon, someone with a new method of study will demonstrate these connections.

My life has taught me one most important fact: that which is true is that which is best. I believe my observations to be the beginning not the end of knowledge of life. Those who follow me can, through objective inquiry, dispel the darkness of ignorance which I see all around me. There is much which is yet unknown. I have done little more than mark the break of the modern spirit with the old traditions. No longer should men be content with careful observation and with ac-

curate description; no longer should men be content with finely spun theories and dreams which serve as a common subterfuge of ignorance.

To the age of the hearer, in which men have heard and heard only, has succeeded the age of the eye, in which men have seen and have been content with seeing only. But at last has come the age of the hand, the thinking, devising, planning hand; the hand as an instrument of the mind. I believe that knowledge today indicates only the beginning of the understanding of life, for knowledge like an arrow moves only in one direction, except in the minds of some men.

I thank you for listening to an old man.

Postscript: Dr. Harvey died in his eightieth year on June 3, 1657, of apoplexy. It is inscribed on his tomb that he was "full of years and fame."

A gifted contemporary of his, Abraham Cowley, managed to sum up in five charming lines the epitome of Harvey's life, work and influence:

"Harvey sought for Truth, in Truth's own book,
The creatures, which by God himself was writ;
And wisely thought 'twas fit,
Not to read comments only upon it,
But on th' original itself to look."

CLINICAL CONFERENCE

Editor: EDGAR V. ALLEN, M.D.

Associate Editor: RAYMOND D. PRUITT, M.D.

Coarctation of Aorta Complicated by Bacterial Endocarditis and an Aneurysm of the Sinus of Valsalva

By FRANK GLENN, M.D., HAROLD J. STEWART, M.D., MARY A. ENGLE, M.D., DANIEL S. LUKAS, M.D., JOSEPH ARTUSIO, M.D., ISRAEL S. STEINBERG, M.D., AND GEORGE R. HOLSWADE, M.D.

DR. FRANK GLENN: The patient for today's discussion presented some particularly interesting and challenging problems when she was first seen at The New York Hospital in November 1954. I am going to ask our panel to review with you the ideas and considerations that confronted us in the diagnosis and management of this patient's heart disease. Dr. Engle, will you please give us the history?

DR. MARY A. ENGLE: The patient, a 27-year-old married woman, was admitted for evaluation of coaretation of the aorta. From her and from the physicians who took care of her from infancy we obtained the following information. She was born 1 month prematurely. Because she failed to thrive, she was taken to a pediatrician at the age of 5½ months. He discovered a loud systolic murmur all over the precordium and in the lung fields. The aortic and pulmonic second sounds were distinct, and there was no precordial bulge. Fluoroscopy disclosed enlargement of the left ventricle. These findings remained unchanged throughout infancy and childhood and she was considered to have a ventricular septal defect.

Failure to thrive was most marked during the first year. After the age of 2, however, she began to improve and by the age of 9 years she was average in size (fig. 1). She tired after exercise and became short of breath more quickly than her playmates. Restriction of activities was advised by the physician. At this time she had a murmur of aortic insufficiency. The first recorded blood pressure determination was at age 12, measured at 165-145/65 mm. Hg in the arm.

In 1947 the patient had fever and blood culture was positive for *Streptococcus viridans*. The blood pressure in the arms was 210/70 and in the legs 122/80 at this time. She received a course of penicillin for 2 weeks. She suffered a second episode of *Str. viridans* infection in 1954. This was treated with intravenous penicillin and streptomycin for 6 weeks. The diagnosis of coaretation of the aorta was made at this time. The cardiothoracic ratio at this time was 53.4 per cent.

DR. GLENN: Dr. Engle, is this the usual course of events for a patient with coaretation of the aorta?

DR. ENGLE: Yes, it is a common story. The patient with coaretation of the aorta is apt to have difficulty from his lesion at 2 age periods: early infancy and early to mid-adult life. Babies may fail to thrive and even go into heart failure in the first months of life. The early difficulties seem related to the severity of the coaretation as well as to the relationship of this constriction to the ductus arteriosus, which is normally still patent in the newborn period. Medical management of the heart failure is quite successful in tiding those babies over the period of early difficulty

From the Cardiovascular Conference Group made up of members from the various departments of the New York Hospital-Cornell Medical Center: Surgery, Frank Glenn, George R. Holswade; Medicine, Harold J. Stewart, Daniel S. Lukas; Pediatrics, Mary Allen Engle, Henry P. Goldberg; Radiology, Israel Steinberg, Nathaniel Finby; Anesthesiology, Joseph Artusio; Obstetrics, Curtis L. Mendelson.

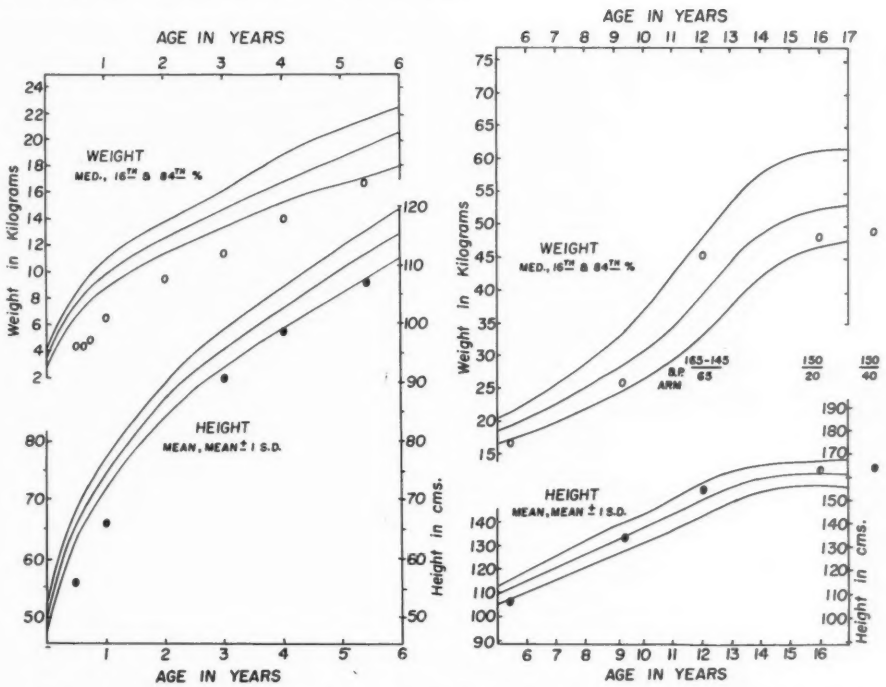

FIG. 1. Growth chart of patient V.W. Failure to grow was most marked during first year. After age 2 it improved and by age 9 was in the average range. Blood pressure in arm at 12 years was 165-145/65 mm. Hg; at 16 years, 150/20; and at 18 years, 150/40. (We are indebted to Drs. Benjamin Kramer and Charles Shookof for supplying the information on this patient's childhood and adolescent years, including growth data.)

until adequate collateral circulation develops. This is usually achieved by the age of 2 years. This particular patient was not in heart failure but she did have cardiac enlargement at least from 5 months of age and her growth was markedly retarded for the first year.

It is interesting that adults may not volunteer such a history even though this was a difficult time in their lives. It is a period beyond their memory, and unless a parent or the physicians' notes are available, as in the present case, this part of the history may be lost.

DR. GLENN: Dr. Stewart, if these children survive childhood, in brief, what may be the course of their disease?

DR. HAROLD J. STEWART: Certain patients live a normal life span and die of some disease not related to the congenital defect. On the other hand during adulthood, patients with coaretation of the aorta are subject to several complications: (1) to subacute bacterial endarteritis or endocarditis, which may occur on the additional lesion of bicuspid aortic valve, (2) to rupture of the aorta, (3) to a cerebral vascular accident, (4) or to the manifestations of hypertensive cardiovascular disease, and perhaps heart failure, (5) heart failure or rupture of the aorta, or of a cerebral aneurysm, may result from the increased burden of pregnancy.

DR. GLENN: Let us return to the case presentation. What were the pertinent findings on examination when this patient came under observation here?

DR. ENGLE: Physical examination revealed strong radial pulses and weak femoral pulses with a perceptible lag behind the radial impulse. Blood pressure in the arms was 190/50-0 and in the legs 95/40 mm. of Hg. A bounding pulsation was visible in the suprasternal notch, and pulsations could be

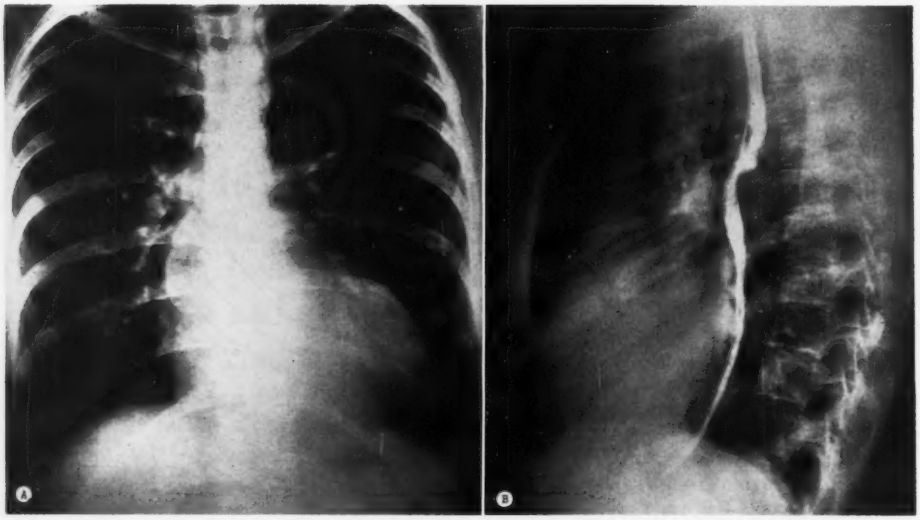

FIG. 2. Roentgenograms. *A*. Frontal, showing enlargement of left ventricle, lack of aortic knob prominence, and rib notching. *B*. Lateral, showing anterior displacement of esophagus by enlarged ascending aorta.

seen and felt over the chest posteriorly. There was no cyanosis or clubbing of fingers or toes. The heart was enlarged to the anterior axillary line. A systolic thrill was palpable over the aortic area and in the suprasternal notch. A loud, long systolic murmur, maximal in the second right interspace, was transmitted to the neck vessels and the aorta, over the precordium, and to the chest posteriorly. A separate harsh systolic murmur was heard in the fourth and fifth left parasternal spaces. A long, blowing diastolic murmur along the left sternal border originated at Erb's point. The lungs were clear, the liver and spleen were not enlarged, there was no peripheral edema, and embolic phenomena were not detected.

Laboratory studies showed normal red blood cell count, hemoglobin, and hematocrit level, but the white blood cell count was 12,500 and the sedimentation rate was elevated. Three blood cultures were negative.

X-ray and fluoroscopy of the chest (fig. 2) revealed a cardiothoracic ratio of 60 per cent. The enlargement was predominantly left ventricular, though there was some enlargement of the left atrium as well. The aortic knob was normally prominent. In the left anterior oblique projection the ascending aorta was dilated and widely pulsatile. Barium swallow confirmed the left atrial enlargement and disclosed an anterior displacement of the esophagus by a dilated portion of the ascending aorta. This was thought (and later shown by angiocardiography) to be due to the poststenotic dilatation of the aorta below the coarctation. There were no other retroesophageal vessels, suggestive of aneurysmally dilated intercostal arteries. Rib notching was present bilaterally.

An electrocardiogram disclosed a pattern of left ventricular hypertrophy (abnormally tall R waves in the left precordial and foot leads with deep S waves in the right precordial leads) and of left ventricular "strain" (depression of S-T segments and inversion of T waves in left precordial and foot leads with reciprocal changes over the right side of the precordium).

DR. GLENN: Dr. Lukas, will you give us the pressure measurements you made?

DR. DANIEL S. LUKAS: Intra-arterial pres-

sure tracings were characteristic of coarctation of the aorta and aortic insufficiency. Measurements were 227/63 (mean 122) mm. Hg in the arm and 110/66 (mean 82) in the leg.

DR. GLENN: Dr. Stewart, will you comment on the diagnosis at this point?

DR. STEWART: Dr. Glenn, I think that the diagnosis of coarctation of the aorta was readily made clinically in this patient. The volume of all the peripheral pulses should be estimated clinically in every patient and the diagnosis should be suspected when the volume of the pulses in the legs is less than that in the arms, or may indeed be absent. Moreover, the blood pressure should be taken not only in both arms but also in both legs in every patient in all age groups.

The following findings pointed to this diagnosis: 1. The volume of the radial pulses was greater than the femoral pulses. 2. The blood pressure in the arms was higher than in the legs, indicating an obstruction to the flow of blood through the aorta below the subclavian artery. It may be said parenthetically that the blood pressure may be normal in the arms, but decreased to absent in the legs. The carotid pulsations were exaggerated as were the aortic pulsations in the suprasternal notch. 3. The peripheral signs of collateral circulation shown by pulsations and bruits over intercostal arteries posteriorly and other collateral vessels used to carry arterial blood from above the coarctation back into the aorta below the obstruction. 4. The x-ray of the chest showed notching or scalloping of the lower margins of the ribs by the dilated tortuous intercostal arteries. Both the pulsations and notching may be absent in children. The presence of these latter 2 signs is a valuable guide to the surgeon as to the possibility of a successful operation because of the availability of these vessels to maintain circulation while the aorta is clamped. The x-ray showed left ventricular enlargement and absence of the aortic knob. 5. The exact location of the coarctation and the amount of proximal segment beyond the subclavian available to the surgeon for the repair was demonstrated by angiocardiogram, which Dr. Steinberg will discuss shortly.

Perhaps Dr. Engle has some additional comment to make.

DR. ENGLE: Localization of the coarctation was possible from the studies thus far presented. The fact that the pulses in the neck and in both arms were equally strong placed the obstruction distal to the left subclavian artery. There was evidence on barium swallow of a large retroesophageal vessel below the level of the descending aortic arch (fig. 2*B*). In such a patient this deformity of the esophogram is due to the poststenotic dilatation of the aorta just beneath the coarctation. Thus the narrowed segment of aorta was localized to the area of the aorta where it most commonly occurs: at the level of the ligamentum arteriosum. One additional localizing sign that is useful is the smooth, blowing, well-localized systolic murmur that is heard posteriorly near the midline overlying the narrowed segment. If one listens along the course of the descending aorta, such a murmur can often be detected, even if the coarctation is in the abdominal aorta. This patient, however, had such a loud systolic murmur over her chest anteriorly and posteriorly that this sign was less valuable.

Coarctation of the aorta is much less common in females than in males. When it is present, it is apt to be in an unusual location or complicated by some additional lesion. This patient's coarctation was in the usual location, but the presence of an associated cardiac lesion was suggested by the loud systolic murmur over the heart and chest that were present from infancy. The murmur of a coarctation itself is soft and is heard better posteriorly over the descending aorta than it is over the heart. With enlargement of the left ventricle and dilatation of the mitral valve ring or of the aorta, murmurs of relative mitral insufficiency or aortic stenosis appear, but her murmur was quite loud and unchanging from early infancy, even though her heart was not much enlarged. A more likely ex-

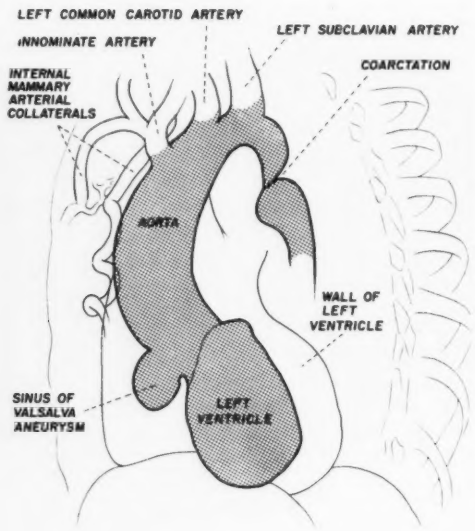

FIG. 3. Left anterior oblique angiocardiogram 7 seconds after beginning the injection. *Left.* X-ray showing hypertrophy of left ventricle, aneurysm of sinus of Valsalva, coarctation of aorta, and internal mammary arterial collateral vessels. *Right.* Tracing of x-ray.

planation is that she had a congenital anomaly of the aortic valve in the form of a bicuspid, slightly stenotic aortic valve or subvalvular ridge. Abnormalities of the region of the aortic valve are commonly associated with coarctation of the aorta.

DR. STEWART: In my experience the systolic murmur in adults is heard best anteriorly over the base of the heart. If it is very loud, it may be heard posteriorly as well but it is difficult to be certain whether a murmur heard posteriorly may not be bruit over the collateral circulation.

The murmur of aortic insufficiency had been heard in this patient at 12 years of age before she had subacute bacterial endocarditis. It is not uncommon to hear such a murmur in these patients in the absence of any complication. I have thought that the murmur was due to dilatation of the aortic ring by the dilatation of her aorta with the hypertension above the coarctation. Murmurs are not heard in "normal" bicuspid aortic valves.

DR. GLENN: The history and findings given by Dr. Engle justified the diagnosis of coarctation of the aorta, aortic regurgitation, and bacterial endocarditis. Demonstration of the exact location of the coarctation enables the surgeon to plan his approach as well as to be forewarned of additional possible abnormalities.

Dr. Steinberg, will you review the x-ray findings including the angiocardiograms of the patient?

DR. ISRAEL STEINBERG: The conventional roentgenograms showed left ventricular enlargement. There were absence of the aortic knob and posterior indentation of the esophagus by a dilated descending aorta. Rib notching was present bilaterally from the fourth to seventh ribs. Angiocardiography showed coarctation of the aorta at the usual site just below the origin of the left subclavian artery (fig. 3). There was dilatation of the ascending aorta and brachiocephalic arteries, and large arterial collateral vessels were seen. A

2-cm. saccular aneurysm of the right aortic sinus was clearly visualized.

DR. GLENN: Dr. Steinberg, would you tell us something about your experience with aneurysms of the sinus of Valsalva?

DR. STEINBERG: The aortic sinuses are intracardiac and cannot be identified on conventional roentgenography. During angiocardiography they appear as dilatations at the root of the aorta immediately above the aortic valves and are best visualized in the left anterior oblique view. Inconstant filling of the coronary arteries during angiocardiography does not always allow individual identification of the sinuses. However, in the left anterior oblique view the right coronary sinus is regularly anterior to and just behind the sternum. The aortic sinuses are in close relation to all the cardiac chambers, particularly the right atrium and ventricle. The origins of the pulmonary artery, the interventricular septum, and the left atrium are adjacent, whereas the superior vena cava is more distant.

Aneurysms of the aortic sinuses (of Valsalva) are rare and are either congenital or acquired. The acquired types are chiefly due to syphilis or bacterial endocarditis. The congenital aneurysms are thought to be due to a development defect in either the aorticopulmonary septum or the elastic tissue of the aortic sinuses. Edwards and Burchell attribute congenital aneurysms to lack of continuity between the aortic media and aortic ring. In aortic sinus aneurysms the wall is made up of the atrium instead of aortic media; pressure within the aorta causes bulging of the sinus, producing an aneurysm.

In an 11-year period, during which over 1,000 patients were studied by the intravenous method of angiocardiography, 25 cases of unruptured aneurysms of the aortic sinus have been diagnosed at this center. Ten were acquired; 9 were due to syphilis and 1 was due to arteriosclerotic dilatation of the thoracic aorta. Fifteen were congenital and of these 6, including the case herein presented, were associated with coarctation of the aorta. One patient had aneurysmal dilatation of the aortic sinuses and pseudocoarctation of the aorta while another had associated aortic and mitral valvular disease. Seven patients had arachnodactyly. Aneurysmal dilatation of the aortic sinuses was found in all the cases except the one reported here; in this, the right aortic sinus alone was aneurysmal.

Aortic regurgitation, which is common in patients with aortic sinus aneurysms, has been attributed to dilatation of the aortic ring and was present in all the acquired cases of aortic sinus aneurysm. In congenital aortic sinus aneurysms, anomalies of the aortic cusps have been frequent at autopsy. In our series, in addition to the case described above, aortic incompetence occurred in a patient with arachnodactyly.

Congenital aortic sinus aneurysms are paper thin and have a tendency to rupture into the structures of the right side of the heart. When perforation occurs, severe overloading of the right cardiac chambers, pulmonary hypertension, and intractable heart failure follow. Sudden onset of dyspnea associated with a machinery murmur suggests rupture of the aortic root with creation of an aorticocardiac fistula. Confirmation of this event may be obtained by cardiac catheterization.

The incidence of aneurysm of the aortic sinuses in coarctation of the aorta is difficult to estimate; it occurred 6 times among 128 patients with coarctation of the aorta studied angiocardiographically at this center. The ages of patients varied from 13 to 27 years with an average of 21 years. Five were males and 3 females. Only 1 was a Negro. Three patients were asymptomatic although a history of previous hypertension or heart murmurs was present in every instance. Headache was present in 2, while 1 had bacterial endocarditis. Systolic murmurs (grade III to IV) transmitted to the axilla and back, especially over the suprascapula area and similar to those usually found in coarctation of the aorta, were common.

In all cases of aneurysmal dilatation of the

aortic sinuses and coaretation there was enlargement of the heart, especially the left ventricle. Deformity of the aortic arch and rib notching were constant findings. Angiocardiography provided the definitive diagnosis of aortic sinus aneurysm and demonstrated the point of coaretation. In the literature there is also a report of a right aortic sinus diagnosed by retrograde aortography.

DR. GLENN: Thank you. That is a beautiful demonstration.

Dr. Engle, will you tell us more of her hospital course?

DR. ENGLE: While these studies were being performed, the patient ran a low-grade fever, around 37.6 C., and had a persistently elevated white cell blood count and sedimentation rate. The possibility of incomplete cure of the subacute bacterial endocarditis was raised.

DR. GLENN: Dr. Stewart, what should be done to evaluate such a situation? What therapy would you recommend for bacterial endocarditis?

DR. STEWART: A persistent search should be made for embolic manifestations: peripheral petechiae in nailbeds, fingertips, eyegrounds; repeated blood cultures at the height of the fever. Arterial blood cultures have not been more effective in securing positive blood cultures than venous blood. The most common organism that causes subacute bacterial endocarditis in this defect is the *Streptococcus viridans*. Should the blood culture be positive, an optimal course of therapy should be instituted.

It is the general experience that more relapses occur in patients treated for the shorter periods and with the smaller dosage schedules. Accordingly one starts out on a 6-week program of a total of 4 to 6 million units of sodium penicillin G every day, given in divided doses at 2-hour intervals intramuscularly. If later tests indicate that the strain of the organism is a nonresistant one, the amount of penicillin is increased. On occasion the treatment may be stopped at 4 weeks.

If there is need for attempting to treat for a shorter period, a rapid 2-week "combined" therapy course may be used, namely, a tota of 6 million units of sodium penicillin G intramuscularly in divided amounts every hours, every day, and a total of 2 Gm. o dihydrostreptomycin (or 1 Gm. of strepto mycin and 1 Gm. of dihydrostreptomycin) i 4 doses intramuscularly as originally de scribed by Robbins and Tompsett.

If repeated blood cultures are negative bu subacute bacterial endocarditis is still likely or suspected, a course of therapy should b given. Since 1 out of 5 instances of subacut bacterial endocarditis with positive blood cul tures is due to enterococcus, it is best to trea those with negative cultures as though they are of this worst type and give the combined therapy for a period of 6 weeks.

DR. GLENN: Dr. Stewart, will you pull together the diagnosis that finally emerged?

DR. STEWART: It was apparent that the patient had coaretation of the aorta with very high blood pressure above the coaretation, but with good collateral circulation. There was the murmur of aortic insufficiency. The angiocardiogram showed the coaretation to be located below the left subclavian artery, and also demonstrated an aneurysm of the sinus of Valsalva. The patient had had 2 episodes of bacterial endocarditis or endarteritis, the last one fairly recently. There was no way of ascertaining whether the sinus of Valsalva was the site of the implantation, or perhaps an associated bicuspid aortic valve, or the coarcted segment.

She was a patient with a complicated background who was presented for correction of the coaretation of the aorta.

DR. GLENN: We anticipated 2 hazards in particular with this patient. The first was that an increase in the blood pressure following the application of occluding clamps prior to resection of the coarcted segment might result in a rupture of the aneurysm of the sinus of Valsalva. The second was the possible requirement of prolonged occlusion of the aorta because of technical difficulties that might arise from the result of a long-standing infection, the bacterial endocarditis.

Dr. Stewart, how soon is it safe to operate

fter recent subacute bacterial endocarditis?

DR. STEWART: Dr. Glenn, with this patient vith slight fever only, who had coarctation f the aorta with very high blood pressure nd an aneurysm of the sinus of Valsalva, he possibility of its rupture indicated that epair of the coarctation, if it could be done, hould be carried out as soon as possible.

To this end she was given a 2-week course f penicillin therapy and was discharged afebrile on December 6. Because of nocturnal ough, dyspnea, and orthopnea as evidence of arly heart failure, the patient was digitalzed. She was readmitted on February 13, pproximately 2½ months later. This period f time was allowed to permit healing of the ndocarditis and formation of strong scar issue in the aneurysm of the sinus of Valsalva n case this was involved.

DR. GLENN: Dr. Artusio, what problems does this patient present to the anesthesiologist?

DR. JOSEPH ARTUSIO: We have used diethyl ether in this clinic to accomplish a light level of anesthesia, which we have termed analgesia. The level is one in which there is minimal depression to respiration and circulation, and the patient frequently is oriented as to place but is completely analgesic and has no memory of the experience. At this level of anesthesia the patient has optimal reactivity to the stresses of surgery, blood loss, extreme positions on the operating table, and change of position on the operating table.

Premedication consisted of a small dose of atropine, 0.2 mg., and in order that the circulation not be embarrassed by the presence of an opiate, none was used. A 250-mg. dose of thiopental sodium, in a 2.5 per cent solution, was given for the psychic sedation afforded the patient, so that she would not fear the anesthetic mask. Nitrous oxide-oxygen was started, with an 8-L. flow of 75 per cent nitrous oxide and 25 per cent oxygen, and ether was gradually added to the mixture until the patient entered a light level of surgical anesthesia. At that time, under direct vision, the pharynx and larynx were sprayed with 2 per cent Xylocaine for topical anesthesia, a 38-French cuffed endotracheal tube was inserted into the trachea, and the patient was immediately returned to the analgesic state of anesthesia where she responded to the spoken voice.

Since this patient had an aneurysm of the sinus of Valsalva in association with her coarctation of the aorta, we were most concerned that during the period in which the proximal aorta was clamped the blood pressure should not rise unduly and produce rupture of the aneurysm. It was planned to use Arfonad, a thiophanium derivative, which would induce ganglionic blockade in the periphery and control the height of the blood pressure. However, from previous experience with this compound we knew that the desired hypotension was not always achieved. This resistance to hypotension is particularly true in the young adult group to which this girl belonged. Thus it was considered that if Arfonad did not produce the necessary hypotension, concomitant hypothermia might aid to control blood pressure.

Actually Arfonad worked very well and we were able to reduce the blood pressure at will. The blood pressure before the aortic clamps were applied was 230/80 mm. Hg with a pulse rate of 80. Arfonad was started by intermittent injections of 3 mg. followed by a 0.1 per cent adjustable drip. In this manner the blood pressure was maintained within a range of 140 to 200 systolic. Following the anastomosis the blood pressure leveled off to 170/80.

DR. GLENN: Dr. Holswade, what are the advantages of hypothermia in this situation and how was it used?

DR. GEORGE R. HOLSWADE: It was hoped that by cooling the patient to approximately 32 C. the blood pressure would fall subsequent to a decrease in cardiac output and would not rise precipitously during the occlusion of the aorta. When surface cooling of the body occurs, there is often a short initial rise in blood pressure due in part to peripheral vasoconstriction and possibly to shivering in some cases. But as the cooling progresses, the blood pressure falls in a curve

that is parallel to that of the temperature and to that of the cardiac output. Cooling in a patient such as this should not be carried to a rectal temperature lower that 31 or 32 C. In this temperature range there is little danger of serious cardiac arrhythmias. This degree of hypothermia might provide just enough slowing of heart action, just enough decrease in cardiac output and just enough hypotensive effect to prevent a rupture of the aneurysm of the sinus of Valsalva when the aorta is cross clamped. For this reason it seemed advisable that the patient be cooled while the chest was being opened and the coarctation was being dissected free.

Cooling of the patient did not delay the operation. It was easily accomplished by pumping a cold alcohol solution through special rubber blankets (Thermo-rite), which were placed beneath the patient and over the lower portion of the body. To further speed up the cooling process plastic bags filled with crushed ice were packed around the patient. The temperature was reduced to 32 C. and maintained at that level until the anastomosis was completed. Warm water at 44 C. was then pumped through the rubber blankets.

The patient remained on the operating table until her body temperature had returned to 35 C. She withstood the procedure extremely well and was awake at the end of the operation.

Dr. Glenn: The operation was accomplished with little more than the usual effort required for an adult with a coarctation. There was a very luxuriant collateral circulation. The intercostal arteries near their origin from the aorta were almost aneurysmal. Three pairs were divided. The internal mammary was very large.

The heart was enlarged, the left ventricle being quite prominent, its wall hypertrophied. The proximal aorta at its origin was enlarged and a coarse thrill was felt in systole, but perceptible in diastole. A saccular aneurysm of the right aortic sinus measured 2.2 cm. in diameter, and projected 2 cm. above the surrounding cardiac surface. It had an egg-shell consistency and expanded very little on contraction of the left ventricle. Probably it was

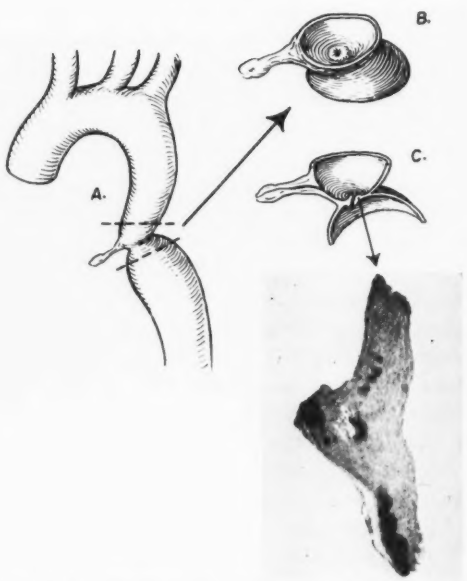

Fig. 4. Findings at operation. *A*. Coarctation located 4 cm. distal to subclavian. Aorta distal to it enlarged, jet plaque palpable 2 cm. beyond on the left lateral aspect of arterial wall. *B*. Ligamentum arteriosum entered coarcted segment proximal to diaphragm. The lumen of the diaphragm was slit-like and measured 2 mm. in its greatest diameter. *C*. Wall of coarcted segment at level of the diaphragm. × 12.

partially obliterated and, in the belief that it might further decrease following the lowering of the blood pressure after resection of the coarctation, it was left unmolested. Furthermore, it has been demonstrated that the intracardiac approach seems to be the avenue of preference.

The coarcted segment measured 1 cm. in length, and in its midportion as it was held forward on slight tension, a diaphragm could be palpated. A palpable thrill was quite evident, with a jet that could be felt most distinctly 2 cm. beyond on the left lateral aspect of the dilated distal segment. Here there was a definite "jet plaque." The ligamentum arteriosum entered the coarcted segment just proximal to the diaphragm. It measured 1 cm. in length and 0.3 cm. in diameter. On palpation it seemed tubular and possibly patent but there was no thrill. It was divided, the aortic half was patent but

the pulmonary portion was obliterated (fig. 4*A*).

Clamps were placed proximal and distal to the coarctation. There was an elevation of the blood pressure from 160/80 to 220/90 mm. Hg. The coarcted segment was resected, and an anastomosis was done. This required almost 30 minutes and during this period the blood pressure, although fluctuating between 210/90 and 130/80, leveled off at 170/80, being controlled with Arfonad. After completion of the anastomosis the distal clamp was removed and then the proximal clamp was gradually released over an interval of 15 minutes. The blood pressure did not fluctuate thereafter and remained at 170/80.

The lumen of the diaphragm in the resected segment was slit-like in shape and measured 2 mm. in its greatest diameter. There were numerous linear bright yellow fibrous plaques in the diaphragm and the adjacent wall of the aorta (fig. 4*B*).

The wall of the aorta was thickened in the area of coarcation and its pattern was somewhat disrupted (fig. 4*C*). At the junction of the thickened portion and the more normal vascular wall there was an atheromatous area consisting of a collection of large mononuclear phagocytes with foamy cytoplasm. Connective tissue was abundant in the wall of the aorta and in the area of diaphragmatic narrowing of the coarctation the usual parallel pattern had disappeared and the fibers were tangled, twisted, and turned upon one another.

Her immediate postoperative course was uneventful and without complications. She was discharged 3 weeks later. At that time the blood pressures were right arm 150/55; left arm, 160/60; right leg, 210/110; left leg, 200/100.

Dr. Engle, what has happened to this patient since she left the hospital?

Dr. Engle: After convalescence she returned to her regular occupation as a free-lance writer. It is now 2½ years since the patient's operation. She states that she has never been so energetic or untiring. She can climb 3 or 4 flights of stairs before her legs fatigue. She does not experience shortness of breath, and she sleeps flat comfortably. She no longer takes a digitalis preparation.

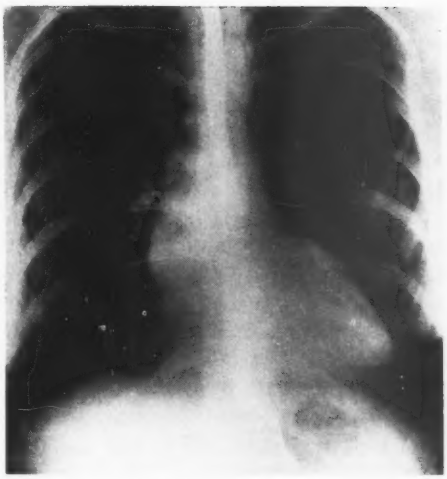

Fig. 5. Roentgenogram 30 months after resection of coarctation showing decrease in size of left ventricle.

Her blood pressure is 130/50 - 30 mm. Hg in the arms and 140/50 in the legs. Exaggerated intercostal pulsations are gone. The aortic systolic murmur and the diastolic murmur of the aortic insufficiency persist. The aortic pulsation in the suprasternal notch is still evident. The heart size is less by 1 cm. than preoperatively, and this improvement is due chiefly to a decrease in left ventricular size (fig. 5). There is no longer evidence of left atrial enlargement, and the ascending aorta is smaller. Her electrocardiogram continues to show left ventricular hypertrophy and "strain."

Thus the manifestations of coarctation of the aorta have disappeared. Relief of this cardiac burden has apparently made her better able to withstand the aortic valve involvement. Objectively, as well as symptomatically, she is better. She will continue under medical supervision.

Dr. Stewart: Dr. Glenn, what has been our experience with aortic insufficiency in coarctation of the aorta?

Dr. Glenn: Aortic insufficiency is seen in coarctation under 3 circumstances. The first is believed to be due to prolonged hyperten-

sion that produces enlargement of the proximal aorta and the aortic ring at the level of the valves. Secondly the aortic valve may have only 2 leaflets instead of 3, and slight enlargement of the aorta may result in insufficiency. Then in the third group there are those instances where disease such as bacterial endocarditis or rheumatic heart disease may cause a loss of valve substance that results in insufficiency. Our experience with aortic insufficiency associated with coaretation of the aorta is limited. We have operated upon 4 such patients. All 4 tolerated the operation well. With a return of the blood pressure to normal, 1 patient lost the signs of insufficiency. Another, although experiencing relief from the preoperative hypertension, continued to have signs of aortic insufficiency and increasing left heart failure, and died almost a year later. The other 2 patients have had a persistence of definite evidence of aortic regurgitation but are definitely improved. This patient, our fifth with aortic insufficiency, continues to have a systolic and diastolic murmur along the left sternal border. Evidently she has a definite aortic regurgitation, now 30 months after operation.

DR. STEWART: During the course of the 30 years of this woman's life, advances in medicine and surgery have come along just in time to help her out of difficulty: antibiotic therapy for subacute bacterial endocarditis and surgery for removal of the coaretation. If she should later need help because of aortic insufficiency or rupture of an aneurysm of the sinus of Valsalva, these conditions too are now within the ever-widening area of cardiovascular lesions, both congenital and acquired, that are amenable to surgery. Close teamwork of the medical and surgical specialties interested in this field has made possible these great steps forward.

Welch, J. S., Kirklin, J. W., Ellis, F. H., Jr., and Bruwer, A. J.: Resection and Grafting for Chronic Occlusion of the Terminal Aorta or Iliac Arteries. J.A.M.A. **164:** 1045 (July 6), 1957.

The recent Mayo Clinic experience in the management of aortic and iliac arterial occlusive disease is described. In the present series of 99 patients, intermittent claudication was the chief symptom and the status of the leg pulses was the most important physical finding. Preoperative aortography was done routinely in order to define the extent of the occlusions. Technical aspects of resection of the obstructed vessels and homograft reconstruction are outlined. Excellent operative results were obtained in 71 patients (72 per cent) as indicated by complete relief of symptoms and return of leg pulses. Five deaths occurred, all postoperatively. The most important factor in the success of this surgery is insuring that the distal anastomosis is made to a patent artery, if necessary to the superficial femoral.

ROGERS

CLINICAL PROGRESS

Effect of Smoking on the Cardiovascular System of Man

By GRACE M. ROTH AND RICHARD M. SHICK

THE smoking of tobacco is a truly American custom, first discovered by Columbus in 1492 when he found the Indians of San Salvador smoking tobacco rolled in maize husks. These primitive cigarettes most likely were the precursor of the modern cigarette. From America the smoking of tobacco was spread quickly by the sailors and merchants to Europe and later to Asia.

After the beginning of colonization of North America by the English, the cultivation and smoking of tobacco by the white man returned to this country from Europe. In the early colonies tobacco was chewed, snuffed, and smoked in pipes. The cigar was not made in North America until 1801, although cigars had been made earlier in Cuba and the first cigar factory had been erected in Hamburg in 1788. With the introduction of the cigar, the tobacco habit changed considerably and cigar smoking became popular. The cigar became the symbol of wealth, substance, and solidity.

The introduction of cigarettes was a slower process; it started in France, proceeded to England and then to the United States by about 1850.

The merits and demerits of tobacco have been the subject of much controversy. Hundreds of books, pamphlets, and poems have portrayed the joys and glory of tobacco and the way to health by its use, while equally as many publications have satirized and virulently condemned the bewitching leaf. Physicians, scientists, philosophers, and men of the world have supported both sides, but sharp differences of opinion still remain.

During the century from 1848 through 1947, the effects of long-continued use of tobacco on the heart and peripheral blood vessels of man were investigated widely. A few of these investigations will be mentioned to show the trends. Graves,[1] in England, as early as 1848 published observations of disturbed heart action produced by heavy smoking. Beau,[2] in 1862, stated that tobacco smoking could initiate angina pectoris under certain conditions. Favarger,[3] in 1887, suggested that nicotine was the most important of the poisons in tobacco smoke. He described chronic tobacco poisoning in detail and stated that the continued use of nicotine initiated coronary spasm by constriction of the coronary arteries. Thus, chronic tobacco poisoning was given as the true cause of heart disease. Even then some doubt arose because some persons 70 to 80 years of age did not have any evidence of chronic tobacco poisoning in spite of heavy smoking for many years. Huchard,[4] another incriminator of tobacco as a cause of heart disease, introduced the term "tobacco angina" in 1899. Plesch[5] disagreed with Favarger and reported that chronic excessive use of tobacco was not the chief cause of heart disease. Still other investigators[6-10] stated that heavy smoking predisposed to arteriosclerosis.

More evidence of the causal role of tobacco in peripheral vascular disease was available, particularly in thromboangiitis obliterans. Although thromboangiitis obliterans and to a less degree coronary heart disease seem to have some statistical relationship to the smoking of tobacco, experimental and clinical evidence indicated that smoking probably was only a contributory factor and not an etiologic one.

Today one of the major medical questions is, "Does smoking really have an effect on the cardiovascular system of man?" It seemed

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wise to review the evidence presented on this question during the last decade and to refer briefly to earlier work whenever necessary.

Substances in Tobacco Smoke and Their Absorption

The 2 substances absorbed in any appreciable amounts from tobacco smoke are carbon monoxide and nicotine. Previously many of the effects of smoking were attributed to carbon monoxide. Now acceptable evidence indicates that carbon monoxide plays little, if any, role in producing the cardiovascular effects, and this leaves nicotine as the most important agent.

The first question that might be asked is how much nicotine is absorbed when a cigarette is smoked? The standard cigarette weighs 1 Gm. and contains 20 mg. of nicotine. According to Baumberger,[11] when a cigarette is smoked, 35 per cent of the nicotine is destroyed at the burning tip, 35 per cent is lost in the side stream and much of this is given off to the environment, 22 per cent enters the mouth through the main stream of the smoke, and the remaining 8 per cent remains in the unsmoked portion of the cigarette. It is estimated that 3 to 4 mg. of nicotine enters the respiratory passages while from 2.5 to 3 mg. is absorbed by the lungs. When the smoke is held in the mouth for 2 seconds and then released, 66 to 77 per cent of the nicotine is absorbed, and when smoke is inhaled, 88 to 98 per cent of the nicotine is absorbed. Thus the amount of nicotine absorbed is dependent on how long the smoke remains in the mouth, whether the smoke is inhaled or not, and the frequency and depth of inhalation.

Weatherby[12] found that vasoconstriction took place after smoking standard brands of cigarettes but that when such cigarettes were denicotinized and smoked, the vasoconstriction was abolished almost completely. Other investigators[13-17] found that vascular effects produced by smoking were similar whether standard cigarettes or commercially denicotinized cigarettes were smoked.

Effect of the Filter. McDonald, Sheard, and Roth[18] reported that the physiologic effects of smoking a cigarette with a filter were not different from those of smoking an ordinary cigarette and smoking a denicotinized cigarette.

Haag, Finnegan, and Larson[19] studied the efficiency of filters in reducing the effects of irritants of the edema-producing type in cigarette smoke. They found that the edema-producing properties of the second and third puffs of smoke from an unfiltered cigarette were significantly less than those of the fifth and sixth or the eighth and ninth puffs. Also, when used the first time, cartridge filters significantly reduced the irritants of edema-producing type contained in cigarette smoke. However, with continued use, their effectiveness was reduced. The investigators stated, therefore, that the development of increasingly efficient filters would have as its culminating achievement a filter that would pass no smoke at all. It is exceedingly doubtful that the average smoker would take kindly to this.

Because of the controversy concerning the production of cancer of the lung by smoking, additional filters have been produced as a measure of protection in removing both nicotine and tars from cigarette smoke. From a survey made by the Chemical Laboratory of the American Medical Association,[20] the following results were found. In all cases the fraction of nicotine removed from the main stream of smoke by the filter is small. The amounts of nicotine and tars assimilated by the smoker are proportional to the amounts that reach a smoker's mouth from the main stream of the smoke. The amounts assimilated cannot be determined easily because of the variations among individuals and the differences in their smoking habits.

Effects of Central Origin on Smoker and Nonsmoker

The nausea and vomiting that may occur when tobacco is first smoked by a nonsmoker are mainly central in origin. Tolerance to nicotine indicated by cessation of these symptoms does take place after repeated smoking. This is evidenced by the absence of

hese effects in habitual smokers. Therefore he actual effect of smoking can be deter-nined better in a habitual smoker than in a nonsmoker.

Effects of Smoking on the Peripheral Circulation

That smoking causes constriction of the peripheral blood vessels, both in normal subjects and more conspicuously in those with peripheral vascular disease, is rather generally agreed. To have a subject smoke and then to determine the effects of the smoking on the peripheral blood flow seem simple. However, all methods of measuring blood flow in man are indirect, and each has its own inherent error. Furthermore, irrespective of the method used, certain fundamental factors concerned with the status of the individual bear directly on the measurement of the blood flow in the extremities. These appear to be the environmental temperature,[21] the position of the subject,[22] particularly of his extremities, the taking of food,[23] and the basal metabolic rate.

To determine changes in blood flow, one of us (Roth) and co-workers used the thermocouple method of Sheard,[24] which measures small changes in the skin temperature electrically. This method was chosen because previous work had demonstrated that the skin temperature of the fingers and toes is the most sensitive indicator of the vasomotor tone of the superficial blood vessels of the extremities. Thermocouples were attached to the fingers and toes to determine any changes before and after smoking. All the factors previously mentioned concerned with the status of the individual were considered in these studies.

At a constant room temperature of 25.5 C. 78 F.) normally the fingers are warmer than he toes, and the temperature of the toes will lepend on the initial basal heat, or the basal netabolic rate. As figure 1 indicates, the skin emperature of the fingers and toes of a man vith rather high basal metabolic rate increases rapidly after a meal. This demonstrates vasodilatation. The skin temperature of the toes particularly of the subject with low basal metabolic rate will increase to the same height after a meal, but it will take longer. For the man with the low basal metabolic rate whose skin temperatures are shown in figure 1, it took 2½ hours to produce the same degree of vasodilatation. The pattern will be the same whatever vasodilating agent is used. If the basal metabolic rate of these 2 individuals were not known, the effects of food would be confusing.

The Smoking Test. Smoking tests were carried out in a constant-temperature room at 25.5 C. (78 F.) and relative humidity of 40 per cent. The subjects fasted for 15 hours before the test. During the tests they wore light-weight, short pajamas and were in a supine position on comfortable beds. Basal metabolic rates were determined before most tests.

At intervals of 10 minutes the temperatures of the plantar surfaces of both first and third toes and the volar sides of the distal phalanges of both first and third fingers were measured by copper constantin thermocouples. The blood pressure, pulse rates, and the basal metabolic rate were determined during the control period. When fairly constant readings of skin temperature, blood pressure, and pulse rate were obtained, smoking was begun. Cigarettes of different brands bought on the open market were used. Two cigarettes were smoked in succession until two thirds of each had been smoked. Simultaneous determinations of blood pressure, pulse rate, and skin temperature were obtained at intervals of 1 minute during the smoking period, which generally lasted 12 to 16 minutes. Observations were continued for 30 minutes to an hour after smoking had ceased.

All the subjects were habitual smokers and inhaled the tobacco smoke with the depth and frequency to which they were accustomed, usually about once per minute. All unnecessary noise and other undesirable stimuli that might cause vasoconstriction were excluded.

Sixty-six standard smoking tests were carried out on 6 normal subjects, 4 physicians and 2 women technicians whose basal metabolic rates ranged from —17 to +1 per cent. These studies showed that the responses to smoking, of the skin temperature of the same individual, varied from day to day according to the basal metabolic rate, but the increase of the blood pressure and pulse rate during smoking varied little from day to day. Thus it was necessary to determine the basal meta-

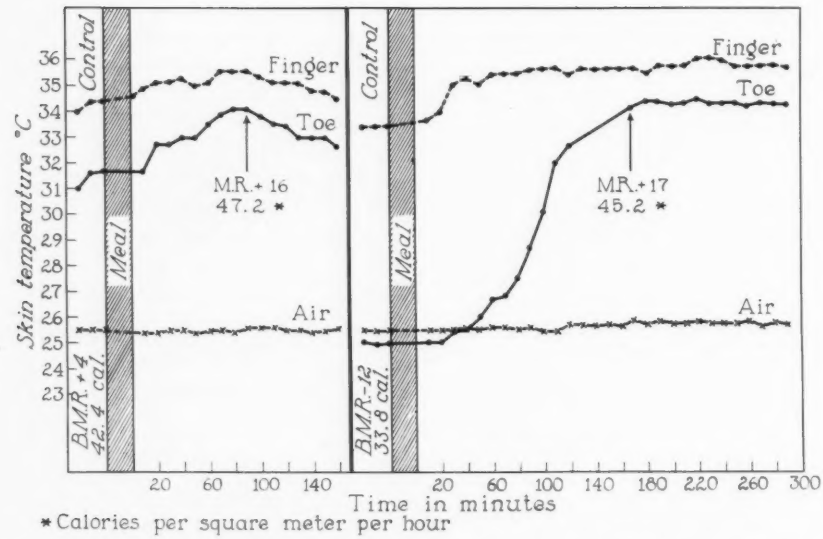

FIG. 1. The increase of the skin temperatures of the toes as well as the metabolic rate after the ingestion of a substantial meal in two normal individuals. *Left.* The subject with high basal heat production. *Right.* A subject with a low basal heat production. The curves show a delay in the rise in the skin temperatures of the toes in the subject with the lower basal metabolic rate. (*Reprinted from Roth, G. M. and Sheard, C.: Relation of basal metabolic rate to vasodilatation and vasoconstriction of the extremities of normal subjects as measured by skin temperatures. Circulation* **1**: *1142, 1950.*)

bolic rate and skin temperatures for each study. On smoking, the skin temperature of the toes of all the subjects decreased an average of 2.5 C. (4.5 F.) with a range from 1 to 4 C. (1.8 to 7.2 F.). For the fingers the average decrease was 3.2 C. (5.8 F.). The average increase of blood pressure during smoking was 20 mm. Hg systolic and 14 mm. diastolic. The pulse rate increased an average of 36 beats per minute, ranging from 20 to 52 beats. The electrocardiographic changes consisted of increased heart rate and decreased amplitude of T waves with inverted T waves in one instance.

Habitual smokers did not show tolerance to the vascular effects of smoking as the skin temperatures of the extremities decreased and the blood pressure and pulse rate increased. The decrease of the skin temperature was not related to the length of time the subject had been a smoker or the number of cigarettes smoked a day.

Two groups of tests were made to determine whether the vascular changes were due to nicotine: 1. Normal subjects received a solution of sodium chloride intravenously as a control and then 2 mg. of nicotine was added to the solution without the subject's knowledge. The skin temperatures decreased rapidly and definitely, the heart rate increased, and the amplitude of the T waves decreased. 2. Thirty smoking tests[25] were carried out on additional subjects with various commercially available denicotinized cigarettes. The vascular effects were similar to those obtained from standard cigarettes.

To determine how much the content of nicotine in a cigarette should be decreased to banish the vascular effects, 192 standard smoking tests were done on 29 normal subjects who were between the ages of 20 and 36 years. The main stream of smoke from 1 cigarette from each of the 6 batches used contained respectively an average of 0.23, 0.55, 1.28, 1.83, 2.47, and 3 mg. of nicotine. As the concentration of nicotine in the main stream of

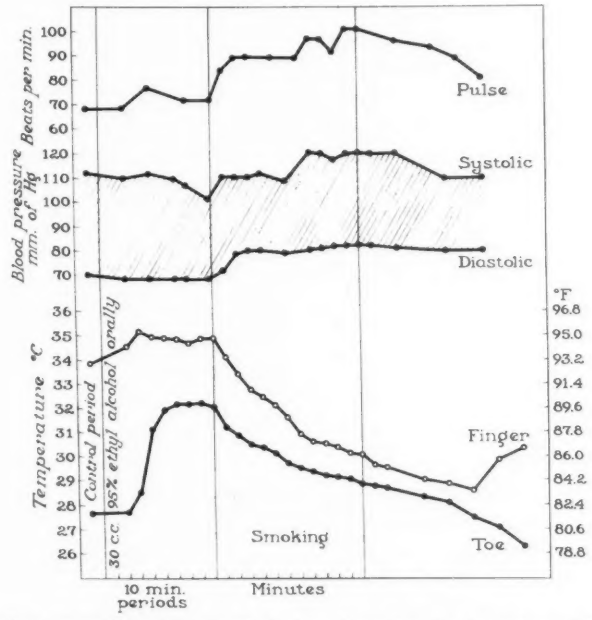

FIG. 2. The effect of smoking two standard cigarettes after the ingestion of 95 per cent ethyl alcohol on the skin temperature of the extremities, blood pressure, and pulse rate. This was the typical response to smoking. (*Reprinted from Roth, G. M.: Tobacco and the Cardiovascular System: The Effects of Smoking and of Nicotine on Normal Persons. Springfield, Ill., Charles C Thomas, 1951, by permission of the Mayo Association.*)

the smoke increased, the skin temperatures of both the fingers and toes decreased until the effects were the same as those from standard cigarettes. The lower the concentration of nicotine in the smoke the less the blood pressure and pulse rate increased from the basal level and vice versa. The increase was sharp when the concentration of nicotine was raised from 0.55 to 1.28 mg. Apparently then, the content of nicotine in a cigarette must be decreased more than 60 per cent from that in a standard cigarette before smoking produces only slight or no vascular effects. The habitual smoker finds the smoking of cigarettes containing so little nicotine unsatisfactory.

Since alcohol[26] taken by mouth will dilate the blood vessels of the extremities in contrast to the constriction from smoking, smoking tests were made on normal subjects and the next day 87 smoking tests were made on the same subjects after ingestion of alcohol. The blood pressure and pulse rate rose definitely on smoking after the ingestion of alcohol in all the subjects. In 72 per cent the skin temperatures of the fingers and toes decreased below the basal level on smoking during the vasodilatation from alcohol (fig. 2). This seems to indicate that the alcohol did not prevent vasoconstriction from smoking.

From 425 smoking tests with tobacco or corn silk[27] on 100 normal subjects who were habitual smokers, the following observations were made: 1. No tolerance develops to tobacco with respect to the vascular effects. 2. An elevation of the blood pressure and pulse rate and a decrease of the skin temperature of the extremities occur only on smoking tobacco. 3. Nicotine appears to be the most important factor in producing the vascular effects. 4. Alcohol does not nullify the effect of smoking.

Recently another investigation by Eckstein, Wood, and Wilkins[28] demonstrated that vaso-

constriction could occur during vasodilatation. These authors reported that smoking 2 cigarettes reduced the blood flow in the foot in 28 of 31 tests. Reductions ranged from 9 to 55 per cent and averaged 22.3 per cent. Smoking in a normal temperature room, a warm room, and also in a cool room caused average reductions in blood flow of 21.7, 23.0, and 20.6 per cent respectively. This striking similarity of response suggests that these different control levels of vasomotor activity do not alter significantly the vasoconstrictor effects of smoking cigarettes. Under the conditions of this study smoking was a less intense vasoconstricting stimulus than cooling the environment from 83 to 68 F.

Returning to the depth and frequency of inhalation of tobacco smoke, Shepherd[29] reported on the effects of cigarette smoking on blood flow through the hand as determined by the plethysmograph. In his opinion the frequency of inhalation of tobacco smoke was most important and has not received enough attention. He chose an inhalation rate of 1 a minute. In studies by one of us (Roth) on the variation in individuals, inhalations were not more rapid than 1 a minute. Shepherd previously had not obtained as great an increase in blood pressure and pulse rate during smoking as our group had, but when 2 of his subjects inhaled at this rate following 15 hours without food and cigarettes, the increases in pulse rate and blood pressure were similar to those obtained by us. The influence of food seems important in all studies concerned with peripheral circulation.

Effect on Peripheral Vascular Disease. The evidence that smoking plays a role in the progression of peripheral vascular disease is no longer controversial. Although it may not be the etiologic factor, it is certainly the most prominent contributing factor. In the series of patients seen at the Mayo Clinic thromboangiitis obliterans rarely if ever was seen in a nonsmoker. Gifford and Hines[30] reported a case of thromboangiitis obliterans in which a 12-year clinical cure was obtained after complete cessation of smoking. Whether the beneficial effect of abstinence from tobacco in thromboangiitis obliterans accrues primarily from arresting the disease process in the arteries and veins, or whether circulation is improved merely by relaxation of unaffected arteries is hypothetical. That abstinence from tobacco is beneficial and should form the primary basis for all treatment in these cases is not hypothetical but is a well-established fact.

Although we discussed filters earlier, we think it important to report further that Friedell[31] has found that men and women are not equally sensitive to tobacco and that the principle of filtration of tobacco smoke is probably a good one and should be used by both men and women. Women evidently need it more than men.

In regard to the new filters, Wright[32] has stated:

> Since at least one of the manufacturers of filtered cigarettes used the results of tests of the laboratory of the American Medical Association in advertising, implying that there is a definite added safety factor, I believe that the following information should be available. During the past years, we have tested a variety of filtered cigarettes as well as the so-called denicotinized cigarettes and have yet to find any that contain tobaccos that do not produce a response in the vascular system as measured by drops in temperature of the finger tips and other determinations. In addition, we have repeatedly observed that relapse in thromboangiitis obliterans may occur when patients smoke the filtered cigarettes. Two days ago, we admitted a patient to the New York Hospital who presents a perfect example of this. This patient first had active thromboangiitis obliterans in 1940. In 1941, he stopped smoking and his symptoms remained quiescent until 1949 when he started to smoke. Within six months gangrene of three toes developed. Once more, on abstinence from smoking and with other therapy, the disease became quiescent, and the man was free from symptoms. About four months ago, impressed by the advertising of filtered cigarettes, he started to smoke filtered cigarettes. Again, his disease has been reactivated, and he has early signs of pregangrenous involvement of the tips of two toes.

In 1950 Rapaport, Frank, and Massell[33] reported that lumbar sympathectomy abolished the peripheral vasoconstriction produced by smoking in the lower extremities of 19 patients. They concluded that the vasoconstriction, therefore, is mediated by sym-

pathetic vasomotor fibers and not by humoral agents such as epinephrine or posterior pituitary hormone. The response was the same whether sympathectomy was performed for thromboangiitis obliterans, arteriosclerosis, or severe vasospasm. One of us (Roth) has likewise found no vasoconstriction as indicated by the skin temperature of the toes during smoking if lumbar sympathectomy was complete, but a considerable fall in the skin temperatures of the fingers occurs during smoking. Thus after lumbar sympathectomy the remainder of the sympathetic nervous system seems to function in a more than adequate manner. This effect can also be seen in the graphs of Rapaport, Frank, and Massell.

Effects of Tobacco on the Heart

Most investigators agree that the effects of smoking tobacco or the intravenous injection of nicotine on the heart are an increase in the pulse rate, an elevation of the arterial blood pressure, and some flattening of the T waves in the electrocardiogram. Two conflicting opinions had developed about 20 years ago: (1) that the changes are due solely to the increased work of the heart and (2) that the changes are due to spasm or constriction of the coronary arteries. In regard to the first, Graybiel, Starr, and White[34] reported in 1938 that undoubtedly a few individuals are susceptible to small amounts of nicotine absorbed during smoking. They suggested that the occasional attacks of angina pectoris precipitated by smoking (tobacco angina) are not the result of coronary vasoconstriction but of a sudden increase in the work of the heart as shown by the increase in blood pressure or heart rate or both.

In the present year further work has substantiated this opinion in regard to the increased work of the heart. Kien, Lasker, and Sherrod[35] determined the effect of cigarette smoke on the open chests of dogs during pentobarbital anesthesia by measuring blood pressure, cardiac output, coronary blood flow, cardiac oxygen consumption, cardiac work, and the electrocardiographic effects. Immediately after the administration, by a specially calibrated smoking device, of 1,200 to 1,500 ml. of cigarette smoke from a standard "king-sized" nonfiltered cigarette, the heart slowed briefly but markedly, and a sustained pressor response followed. These effects were attributed to autonomic ganglionic stimulation by the nicotine absorbed from the cigarette smoke. The "time course" of the hemodynamic responses indicated an early increase in cardiac work that extended for 3 minutes. The coronary blood flow was increased in relation to the rises in both blood pressure and cardiac output. No independent action of cigarette smoke on the coronary vessels was observed. The coronary arteriovenous oxygen difference decreased markedly at first and then increased for a long time. As a consequence, the cardiac oxygen utilization was reduced initially during the period of greatly increased cardiac work and then increased and remained high. These alterations were explained on the basis of metabolic changes in the myocardium. In addition there were extreme electrocardiographic alterations with the changes in oxygen utilization during the period of increased cardiac work.

Until recently it has not been possible to measure the effect of nicotine on the coronary blood flow in man, but it has been shown that nicotine decreases the blood flow in the coronary arteries of the dog. Bellet, Kirshbaum, Meade, and Schwartz[36] administered nicotine to dogs before and after ligation of a coronary artery. After the ligation only a fourth as much nicotine as before operation was required to produce marked electrocardiographic changes.

Travell, Karp, and Rinzler[37] recently studied the electrocardiographic effects of nicotine on 12 normal rabbits and 16 cholesterol-fed rabbits with coronary artery disease. Nicotine caused sagging depression of the S-T segment in about 10 per cent of the rabbits with coronary artery disease. Occasionally lowering of the T waves occurred, but this may occur spontaneously in rabbits. Perfusion of the isolated hearts of rabbits with atherosclerosis showed a higher coronary flow, slower heart rate, and lower amplitude of contraction than in normal hearts. Nicotine in graded doses

injected directly into the perfusion system produced a diminution in coronary blood flow in the perfused hearts that previously had been made atherosclerotic.

In contrast West, Guzman, and Bellet[38] working on dogs catheterized the circumflex or anterior descending branch of the left coronary artery via one carotid artery and cannulated the coronary sinus via one external jugular vein. From 0.25 to 0.5 mg. of nicotine per Kg. of body weight was injected into the coronary arteries. Small doses of nicotine produced a definite decrease in myocardial contractility but no other discernible effects. Larger doses increased coronary flow and myocardial contractility without any change in systemic blood pressure and heart rate. These effects were completely blocked by tetraethylammonium bromide. Still larger doses of nicotine elicited the coronary chemoreflex (Bezold-Jarish) accompanied by decrease in coronary blood flow. These effects were abolished by bilateral vagotomy. West, Guzman, and Bellet concluded that there was no evidence of coronary constriction following administration of nicotine and that the explanation of the effects was the presence in the heart of parasympathetic and sympathetic ganglia and chemoreceptors influenced by nicotine.

In 1957 the first studies using direct catheterization of the coronary sinus and a needle in the femoral artery were carried out on human beings by Bargeron and co-workers.[39] From studies on 30 adults they found that smoking a cigarette caused a significant rise in coronary blood flow and heart rate, a significant decline in coronary vascular resistance and myocardial extraction of oxygen and glucose. In normal subjects smoking did not produce constriction of the coronary blood vessels. As yet the various investigators do not agree completely.

The work of Burn and his co-workers[40-42] on man presents an entirely different view in regard to coronary vasoconstriction. They[40] and Walker[41] found that smoking 1 or 2 cigarettes had an antidiuretic effect for 1 to 3 hours in man. An injection of nicotine (0.33 to 1 mg.) had a similar antidiuretic effect. According to them the inhibitory effects of both smoking and nicotine were accompanied by a rise in the total excretion of chloride, an effect characteristic of the action of the posterior pituitary hormone. In 1951 Burn and Grewal[42] stated that the posterior pituitary hormone is excreted in the urine after 1 or 2 cigarettes are smoked. Thus Burn and Grewal concluded that smoking may produce coronary constriction in man as a result of the release of posterior pituitary hormone.

In the present decade, the electrocardiograph or the ballistocardiograph, or in a few instances, both have been employed in the study of the effects of smoking on the heart of man.

Electrocardiographic Findings. To determine whether smoking of tobacco produced a spasm of the coronary arteries as a result of transient myocardial impairment, von Ahn[43] produced hypoxia in the myocardium and in turn coronary insufficiency by the inspiration of oxygen-poor gases. He found that tobacco smoking or injection of nicotine during hypoxia increased the heart rate and the amplitude of the P waves, flattened the T waves, and caused slight depression of the S-T segments. These electrocardiographic changes were due chiefly to increased sympathetic tone. In studying the origin of these changes, he found that dihydroergotamine counteracted the effect of nicotine on the electrocardiogram, whereas atropine led to approximately the same degree of flattening of the T waves as nicotine. There was practically no flattening of T waves or depression of S-T segments after elimination of the increased heart rate due to smoking or injection of nicotine. Physical work during hypoxia led to more marked flattening of the T waves and depression of the S-T segments than did nicotine under the same condition. In certain cases heavy smoking or injection of nicotine resulted in flattening of the T waves without simultaneous increase in heart rate. This was probably due to increased adrenal secretion. Von Ahn concluded that it is unlikely that the electrocardiographic changes provoked by

smoking or injection of nicotine during hypoxia in persons with clinically healthy hearts were of coronary origin, but that they were probably secondary to increased heart rate.

Ballistocardiographic Findings. The ballistocardiograph records the stroke volume of the heart as a means of determining the cardiac output. Starr[44] almost 20 years ago set up the normal standards and various modifications of ballistocardiograms. Ten to 14 years later Starr and Hildreth[45] tested 67 of the same individuals and determined the effect of aging hearts and of the development of disease in these previously healthy persons. They conceived the idea that the weakening heart has a recourse open to it that has not been realized. By changing the manner of systolic ejection of blood so that acceleration is kept at a minimum, the load of the heart is lifted more slowly, and by this means a heart lacking in strength can maintain its cardiac output unimpaired. It is this change in cardiac function that can be detected from the change in the form of the ballistocardiogram seen so clearly as age advances. And since this adaptation will leave the heart's main function, that of pumping blood essentially unimpaired, it provides an explanation for the observation that the ballistocardiogram will indicate an abnormality early in the course of disease before the development of symptoms or other evidence of cardiac dysfunction.

Dock,[46] in discussing Starr's paper, pointed out that smoking in some persons can change the ballistocardiogram and the changes produced may be identical to those seen after coronary accidents and in older people who are aware of heart trouble. He emphasized, therefore, that tracings must be taken under basal conditions.

The introduction of the ballistocardiograph stimulated various workers to further study of the effect of smoking on the heart. In 1947, Boyle and co-workers[47] used the ballistocardiograph in order to determine the effects of nicotine on the heart in normal persons and in patients with cardiovascular disease. The variations in responses were similar; severe reactions depended on individual susceptibility rather than on the presence of disease. In some patients with heart disease injection of nicotine induced coronary insufficiency that could be the result of constriction of the coronary arteries or of increased work of the heart or of both.

Levy and associates[17] studied the effects of smoking of regular and commercially denicotinized cigarettes on a normal group and a cardiac group. In both groups the systolic and diastolic blood pressures as well as the heart rate increased slightly, but the average cardiac output did not change. The form of the electrocardiogram changed in less than half of the subjects in each group.

Dock and co-workers[48] commented that pathologic patterns were rarely encountered when ballistocardiographic tracings were made with the breath held as was usual with the Nickerson table used by Levy and his group.

Mandelbaum and Mandelbaum,[49] in 1951, used a high-frequency recording ballistocardiograph during normal breathing on 100 consecutive subjects without heart disease. Only 3 ballistocardiograms from the subjects less than 50 years of age were abnormal after smoking, while approximately 43 per cent of those from older persons showed some abnormalities. Among patients with coronary heart disease and hypertension, the incidence of abnormal ballistocardiograms on smoking was much greater. In 1952, the Mandelbaums[50] again reported that 28 per cent of 50 normal subjects less than age 40 responded abnormally to smoking as indicated by the ballistocardiogram. In persons with heart disease the incidence of abnormality after smoking was more than twice this number. The Mandelbaums regarded as significant the fact that of 35 patients with heart disease whom they induced to abstain from smoking, 30 obtained symptomatic relief.

Caccese and Schrager[51] found that the high frequency recording of the ballistocardiograph was much more sensitive than the electrocardiogram to the effect of nicotine on the

heart. Smoking produced mild alterations in the ballistocardiograms of 18 of 31 subjects (23 normal) and great changes in 7 (4 normal).

Scarborough and associates[52] did not consider the ballistocardiogram a good diagnostic test for use on resting persons suspected of having coronary disease because the same abnormalities were found in about 75 per cent of patients given a clinical diagnosis of coronary disease and in 25 per cent of a normal control group of corresponding age.

Henderson[53] in England reported that after smoking all 50 healthy young persons studied had normal ballistocardiograms in spite of an increase in average pulse rate, whereas 10.3 per cent of 30 older persons believed to be healthy had temporarily abnormal ballistocardiograms. In 38 per cent of 40 patients with coronary heart disease and in 4 patients without coronary heart disease but suffering from diseases in which coronary heart disease is a frequent complication, ballistocardiograms became abnormal or more abnormal in form on smoking. Henderson concluded that unusual cardiac sensitivity to nicotine can readily be detected from the ballistocardiogram, particularly in cardiac patients, and that pre-existing coronary artery disease enhances the deleterious effects of smoking on cardiac contraction. He said too that increased work of the heart might often have been a factor in producing relative ischemia, but he suggested, as Burn did, that an outpouring of pituitary hormones is the most likely explanation.

Davis and co-workers[54] reported in 1953 that the high incidence of abnormal ballistocardiograms among older persons limits the value of this method in persons more than 50 years of age. The relative frequency of normal records from those less than 50 years old who have clinical evidence of coronary disease likewise impairs the diagnostic usefulness of this instrument.

After they studied the effects of smoking on 200 subjects, 118 controls and 82 patients with coronary heart disease, by means of the ballistocardiograph, they concluded, however, that the method had diagnostic value as only 6.8 per cent of the normal controls had abnormal ballistocardiograms in contrast to 58.6 per cent of the patients with diseased coronary arteries. This differential margin of 9.1 : 1 was more discriminating than that of any other objective method in separating patients with coronary disease from normal controls. In an extension of their previous work in 1956,[55] they reported the effects of smoking on the ballistocardiograms of 252 normal subjects and 190 patients with coronary artery disease. Changes occurred on smoking in 7.5 per cent of the control subjects in contrast to 48.9 per cent of the coronary group. No abnormality occurred in any control subject who was less than age 40 while abnormalities occurred in only 3 of 89 normal subjects in the fifth decade. Although these figures have a discriminatory ratio of 6.5 : 1, which is less than the 9.1 : 1 ratio of the earlier series, Clough[56] considered them highly significant.

Kelly and co-workers[57] found no abnormalities in the ballistocardiograms in 100 healthy high school lads made during rest and no real ones after smoking. They assumed that the abnormal tracings seen occasionally after smoking represented poor habituation to tobacco.

Simon, Iglauer, and Braunstein[58] reported that the gross changes in the ballistocardiograms of many coronary patients and of some normal subjects more than 30 years of age make it impossible to measure and compare the overall changes in stroke volume and cardiac output that occur after smoking. They found no significant change in cardiac output and in the form of the ballistocardiograms of 17 normal young men following smoking.

In contrast, Buff[59] reported abnormalities in 42 (10 per cent) of 400 ballistocardiograms made after smoking on 250 men and 150 women. All were less than 40 years of age.

In 1956, Strober[60] studied the effect of smoking on the ballistocardiograms of 2,736 male subjects at an air force base. The vast majority of the subjects had normal ballisto-

cardiograms after smoking. Of the 120 smokers in the obese group, 45 per cent had abnormal tracings after smoking, whereas in the nonobese group, 3.6 per cent had abnormal tracings. In regard to obesity Brozek and Keys[61] noted no significant differences in relative weight, arm diameter corrected for subcutaneous fat (as a measure of muscularity), or body density in a group of middle-aged business and professional men who never smoked from those in a group who were heavy smokers. They considered use of either cigarettes alone or all forms of tobacco smoking. However, in a study carried out for 5 years on 17 men who stopped smoking without a superimposed reducing diet the mean weights for 2 years prior to stopping smoking were 75.3 and 75.8 Kg. respectively and increased to 78.4 and 79.3 Kg. in the next 2 years. The increase was statistically highly significant.

Master, Donoso, Pordy, and Chesky[62] carried out studies with the ballistocardiogram on 36 patients less than 50 years of age with uncomplicated peripheral arteriosclerosis or uncomplicated thromboangiitis obliterans; 28 had abnormal ballistocardiograms. Peripheral vascular disease per se, therefore, may produce an abnormal ballistocardiogram at rest in the absence of cardiac disease. When cardiac disease was evident together with peripheral vascular disease in 29 patients at rest, all the ballistocardiograms were abnormal.

Russek and co-workers[63] studied 65 subjects; 28 normal persons who were habitual smokers, and 37 patients with coronary disease. They observed that on smoking, 16 of 28 normal subjects had significant changes in the electrocardiogram and ballistocardiogram, and 2 showed changes closely simulating those of patients with coronary artery insufficiency. No significant improvement in the electrocardiogram or ballistocardiogram was observed in any of these normal subjects as a result of the administration of glyceryl trinitrate. They concluded then that tobacco heart or tobacco angina is not due to underlying cardiac disease but is a definite clinical entity representing functional derangement of this organ due to nicotine. Total abstinence from tobacco was followed by disappearance of all symptoms and electrocardiographic and ballistocardiographic abnormalities.

They also stated that the main effects of tobacco on the cardiovascular system of hypersensitive normal subjects are not due to coronary vasoconstriction but appear more likely to be due to direct myocardial action, or to the effect of nicotine on the cardiac ganglion, or to both. In patients with coronary heart disease glyceryl trinitrate failed to modify or prevent ballistocardiographic changes induced by smoking, while whisky significantly decreased the ballistocardiographic abnormalities after smoking. Because alcohol did not prevent the electrocardiographic changes induced in such patients by a standard exercise test, they concluded that the nicotine response was based primarily on peripheral vascular constriction and not on alterations in coronary blood flow. They were of the opinion that the ballistocardiogram unlike the electrocardiogram was influenced not only by abnormalities in the heart itself but also to an equal or greater degree by changes in the vascular tree. In a strict sense the deterioration of the ballistocardiogram seen in patients with coronary disease after smoking did not seem to be due to hypersensitivity but rather to latent or overt inadequacies in myocardial function brought to light by peripheral vasoconstriction.

A digression will be made to include at this point some earlier work carried out in 1938 by Hines and one of us[64] (Roth) on the effect of smoking on the blood pressure in order to supplement the work of Thomas and her associates soon to be considered. Our study was on 30 normal reactors and hyperreactors and 56 patients with hypertension, as determined by the cold pressor test. In the normal subjects with normal reactions to the cold pressor test the rise in the blood pressure during smoking was 17/8 mm. Hg while in those with hyperreactions it was 30/17. In the patients with hypertension the rise in the blood pressure was 41/23 and in the non-

smokers only 26/9. In the 10 patients with hypertension who had the greatest rise in blood pressure during smoking, the average rise was 47/32. In a more recent group of 40 normal subjects the rise during smoking was from 105/72 to 124/83. In 60 subjects who were hyperreactors to the cold pressor test the rise was 32/21, while in the 10 patients with hypertension the rise was 39/24 or from a basal pressure of 198/130 to 237/154. The conclusion from this study was that the effect of smoking tobacco on the blood pressure of the subjects or patients with inherently hyperreactive vascular systems as measured by the cold pressor test is not due to a nonspecific stimulus acting on a hyperreactive vascular system but is the result, at least in part, of the nicotine in the tobacco, which produces vasoconstriction.

Thomas, Bateman, Lindberg, and Bornhold[65] studied the ballistocardiographic effects of smoking on 113 healthy medical students, 103 men and 10 women, who were 21 to 35 years of age. In both smokers and nonsmokers the systolic and diastolic pressure, pulse pressure, heart rate, stroke volume, cardiac output, and cardiac index showed statistically significant changes on smoking 1 cigarette. The direction and degree of change after smoking varied greatly from subject to subject, so that striking individual differences in circulatory patterns were found.

Subjects whose cardiac output and cardiac index were large to begin with and whose parents had hypertension showed more than twice as great an increase in cardiac output and cardiac index on smoking 1 cigarette as did subjects whose parents did not have hypertension. No such relationship between familial hypertension and hyperreactivity to smoking has previously been described. The studies indicating that hyperreactivity to smoking is related to hyperreactivity to the cold pressor test, and that hypertensive patients react more strongly to smoking than do normotensive subjects are in harmony with the hypothesis that hyperreactivity appears particularly frequently in individuals who are the offspring of hypertensive parents and may be a precursor of hypertension in a given individual. Likewise, subjects with a parental history of coronary disease showed little increase in cardiac output and cardiac index in contrast to subjects with healthy parents.

Statistical Studies. Not many statistical surveys have been made in the past 10 years. Hammond and Horn[66] in 1954 found that in the age group 60 to 65 years the death rate for coronary disease for men who smoked a pack or more of cigarettes a day were twice as high as the rates for men who had never smoked. This was a confirmation of the earlier figures of Pearl.[67]

Doll and Hill[68] in 1956 reported that the mortality rate among British doctors with coronary disease increased progressively with the amount of tobacco smoked. For the group who were more than 35 years of age, the mortality rate was 42 per cent higher in heavy smokers than in nonsmokers.

Sigler[69] reviewed the records of 1,520 patients with demonstrable coronary disease and the anginal syndrome; more than two thirds of them had had at least 1 attack of coronary occlusion. Of this number 985 were living, and 535 dead. Of the 1,186 males in the group, 519 were nonsmokers and 667 smokers. Of the 334 females, 292 were nonsmokers and 42 smokers. Clinical manifestations of coronary disease developed before 50 years of age in 29.2 per cent of the nonsmokers and 44.8 per cent of the smokers among the males, and in only 19.1 per cent of nonsmokers and 50.2 per cent of smokers among the females. The higher the degree of smoking the earlier was the onset of the clinical manifestations of coronary disease. The age at death was also less for smokers than for nonsmokers. Of the males, 20.2 per cent of the smokers and 6.4 per cent of the nonsmokers died before the age of 50 years. Likewise of the females, 46.5 per cent of the smokers and only 5.6 per cent of the nonsmokers died before that age.

Sigler stated that although tobacco may expedite somewhat the development of coronary disease in a small proportion of the population, it is not the sole cause of coronary disease.

Dolgoff and associates[70] studied the smoking habits of 551 men with coronary disease without hypertension and 328 men with hypertension but without coronary disease. These were compared with the smoking habits of 2 matched control groups. No correlation was found between smoking and hypertension. The relative incidence of coronary disease in heavy cigarette smokers was 1½ times as frequent as in nonsmokers and other types of smokers.

Comment

In normal subjects smoking produces a transient increase in the blood pressure and pulse rate, a decrease in the skin temperature of the fingers and toes, and some flattening of the T waves in the electrocardiogram. The values may return to normal in 10 to 15 minutes. Habitual smokers do not show tolerance to smoking by a decrease in these effects. The effect of smoking is not related to the length of time the subject has smoked or to the number of cigarettes smoked.

Since Huchard introduced the term, "tobacco angina" in 1899, some normal subjects have been observed who have been hypersensitive to tobacco, as manifested by changes in the electrocardiogram and ballistocardiogram.[71-73] Some normal subjects even have symptoms on smoking similar to those of coronary insufficiency. Cessation of smoking completely eliminates these symptoms and the changes in the electrocardiogram and ballistocardiogram. Thus tobacco angina or tobacco heart is a definite clinical entity.

For the most part, persons less than 40 years of age rarely have abnormal ballistocardiograms but older persons have abnormal tracings rather frequently. Some young normal subjects with abnormal ballistocardiographic tracings before and after smoking may be the offspring of parents with hypertension or coronary heart disease. Normal subjects who are hyperreactors show greater increase in the blood pressure on smoking than normal reactors do.

In patients with peripheral vascular disease smoking is not the etiologic factor but a most aggravating one. Cessation of smoking for a long time may produce great improvement, but return to smoking can reactivate the disease.

Considerable controversy has existed in regard to the effects of smoking on the heart. These effects are indicated by an increased pulse rate and blood pressure and some flattening of the T waves. Extensive studies have been carried out to determine whether they are due to sudden increased work of the heart or to coronary constriction. The early work on animals was not conclusive. Some workers have suggested that the increase of blood pressure or heart rate or of both reflects increased work of the heart. Confirmation of this has been given by other workers who showed that oxygen utilization by the heart was reduced initially during the period of greatly increased cardiac work and then increased and remained high. The alterations were explained on the basis of metabolic changes in the myocardium. It has been suggested too that constriction of the coronary arteries resulted from the release of posterior pituitary hormone after smoking. Also blood flow in the coronary arteries decreased in arteriosclerotic rabbits after injection of nicotine. In contrast one investigator concluded that the effects of smoking particularly during hypoxia were not due to constriction of the coronary arteries but were secondary to increased heart rate. Another group concluded that injection of nicotine produced no coronary constriction but influenced the parasympathetic and sympathetic ganglia and chemoreceptors in the heart. The first investigators to catheterize the coronary sinus in man concluded that nicotine did not cause coronary constriction but decreased resistance of the coronary vessels and decreased myocardial extraction of oxygen and glucose. Further work with direct catheterization may be expected.

The introduction of the ballistocardiograph added a new approach for study of the effect of smoking. While this instrument is not considered by some workers as being ready for use in diagnosis,[74, 75] it has provided an interesting method for investigation and with

further refinements of the instrument the method may become more critical and practical. Abnormalities may be noted in the ballistocardiograms of patients with peripheral vascular disease without evidence of cardiac disease. Because the ballistocardiogram may be influenced by the entire vascular tree, it is more sensitive than the electrocardiogram to the effects of smoking. It has provided evidence that smoking may not exert its effect on the myocardium or the coronary arteries but mainly on the peripheral blood vessels. In some instances the constriction of peripheral vessels by smoking may point to latent disease of the coronary arteries.

It has been shown too that the cardiac output and cardiac index of normal subjects with hypertensive parents are large before smoking as compared with the controls. On smoking they increased twice as much in normal subjects with hypertensive parents as in the controls, and they increased less in normal subjects whose parents had coronary disease than in the controls.

From the various findings coronary disease seems to occur more frequently and at an earlier age in the heavy smoker than in the nonsmoker.

Summary

In normal subjects smoking or the injection of nicotine produces transient vascular effects on the heart and blood vessels. Apparently tobacco angina or tobacco heart is a clinical entity. Abnormal vascular responses after smoking in normal subjects may be due to hypersensitivity to nicotine, such as occurs in tobacco heart, or to the effect of nicotine on a vascular system demonstrated to be hyperreactive by the cold pressor test.

Tobacco is one of the most prominent contributing factors in thromboangiitis obliterans, as thromboangiitis is rarely found in nonsmokers.

The question as to whether the effects of smoking are due to sudden increased work of the heart or constriction of the coronary artery has stimulated a great amount of research. There is evidence to support both theories.

The findings of abnormal ballistocardiograms before and after smoking in the offspring of hypertensive parents and after smoking in the offspring of parents with coronary heart disease are highly important.

Statistically coronary artery disease seems to occur more frequently and at an earlier age in the person who smokes much than in the nonsmoker. Likewise, the mortality rate is higher among younger persons with coronary disease who are smokers than among those who are nonsmokers.

Summario in Iterlingua

In subjectos normal, fumar o injection de nicotina produce transiente effectos vascular in corde e vasos de sanguine. Apparentemente, "angina a tabaco" o "corde a tabaco" es un entitate clinic. Anormal responsas vascular a fumar occurrente in subjectos normal pote esser le consequentia de hypersensibilitate a nicotina (del genere occurrente in "corde a tabaco") o del effecto de nicotina super un systema vascular que se monstra hyperreactive in le test pressori a frigido.

Tabaco es un del plus importante factores contributori in le causation de thromboangiitis oblitterante, visite que thromboangiitis se trova rarmente in non-fumatores.

Le question de saper si le effectos del fumar es le consequentia de un subite augmento del labor del corde o del constriction del arteria coronari ha stimulate numerosissime investigationes. Il existe datos in supporto del un e in supporto del altere theoria.

Le observationes facite ante e post fumar in le ballistocardiogrammas anormal del progenia de parentes hypertensive e post fumar in illos del progenia de parentes con morbo cardiac coronari possede un alte grado de signification.

Le statisticas pare monstrar que morbo de arteria coronari occurre plus frequentemente e a etates plus juvene in personas qui fuma que in non-fumatores. In plus, le mortalitate inter juvene individuos con morbo coronar qui es fumatores es plus alte que inter ta individuos qui es non-fumatores.

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ABSTRACTS

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BLOOD COAGULATION AND THROMBOEMBOLISM

Bacigalupo, F., Simandl, E., Bhonslay, S. B., and Deterling, R. A., Jr.: The Effect of Heparinization upon Vascular Healing. Arch. Surg. **74**: 153 (Feb.), 1957.

The influence of heparin administration on vascular healing was studied in 21 dogs subjected to a standard operative procedure of anastomosis of the abdominal aorta. The animals were divided into 5 groups and a different method of heparin administration was carried out in each group. In the animals given heparin prior to the anastomosis, leakage through the needle holes at the site of anastomosis occurred, but could be controlled with additional sutures before closure of the abdomen. In no instance was there postoperative bleeding from the suture line. The dogs were killed between the second and twelfth week after surgery and a study of the aorta made in each animal disclosed no impairment of tensile strength or abnormality in healing of the anastomosis. No hematoma developed and wound healing was satisfactory. In a selected series of 6 patients, a course of heparinization was begun immediately following re-establishment of blood flow through bypass grafts inserted for the treatment of segmental arteriosclerotic occlusion of the superficial femoral artery. No complications related to the use of heparin were observed.

Immediate postoperative use of heparin is not recommended in patients with abdominal or thoracic vascular procedures or in cases with synthetic vascular replacements, due to the difficulty in recognizing and controlling bleeding into the thoracic and abdominal cavities and the possible danger of bleeding from a porous synthetic replacement. It is expected that the widest use of immediate postoperative anticoagulant therapy will be in patients with occlusive peripheral vascular disease, since functional results with grafts have been least satisfactory in the smaller arteries.

BROTHERS

Strauss, L., Bay, M. W. and Katz, A. D.: Prothrombin Time during the Postoperative Period. Am. J. Surg. **93**: 95 (Jan.), 1957.

Prothrombin determinations, using a one-stage test, were done on 104 unselected surgical patients undergoing major surgical procedures. Prothrombin determinations were obtained 1 day preoperatively and on the first, second, and third postoperative day routinely. Only 74.6 per cent of the patients had prothrombin values of 70 per cent or over, which was considered normal. Seventy-nine patients showed a fall in the postoperative prothrombin concentration as compared with the preoperative value. Four of the patients with a marked drop in prothrombin activity had clinical phlebitis. This drop may actually be a sign of increased clotting and increased use of available prothrombin. The authors believe that in the presence of suggestive evidence of phlebitis a prolonged prothrombin time is corroborating evidence. In 4 patients, the postoperative prothrombin level was higher than the preoperative value but none of these patients had evidence of phlebitis. Complications occurred in 6 of the 10 patients. A marked drop in the prothrombin time was present in these patients but the same degree of prolonged prothrombin time occurred in cases without complications. There was no correlation between eosinophil response and complications. It is believed that changes in the prothrombin activity may be due to one of several

factors such as liver damage, lack of vitamin K supply, lack of absorption of vitamin K, increased use of vitamin K, inadequate protein nutrition, and response to stress. The authors think that a prolonged postoperative prothrombin time should not be viewed with alarm nor should it provoke an order for urgent vitamin K. Further, they do not believe that large doses of Dicumarol should be given in cases of suspected postoperative phlebitis even with a normal prothrombin time because of the increased sensitivity to Dicumarol during this period.

BROTHERS

Ellis, P. R., Jr., Kleinsasser, L. J., and Speer, R. J.: Changes in Coagulation Occurring in Dogs during Hypothermia and Cardiac Surgery. Surgery **41**: 198 (Feb.), 1957.

In order to determine the cause of bleeding associated with hypothermia, a study was made of coagulation changes occurring in dogs subjected to open cardiac surgery with circulatory occlusion. Laboratory studies included hematologic values, clotting and bleeding times, prothrombin, prothrombin utilization, proaccelerin, proconvertin, fibrinolysin and fibrinogen determinations. The dogs were divided into 4 groups. Group A consisted of 4 dogs subjected to the usual preparation for surgery, including anesthesia, blood vessel cannulation, and intubation. They were also hyperventilated. Group B was made up of 4 dogs who underwent the same preparation as the group A dogs and in addition were cooled to 26 to 29 C. by immersion in ice water for 2 hours, after which they were rewarmed by immersion in warm water. Group C consisted of 15 animals having the same preparation and hypothermia plus open cardiac surgery. Surgery consisted of thoracotomy, 8 minutes of inflow and outflow circulatory occlusion, and creation of an interatrial septal defect. Group D, consisting of 15 dogs, underwent the same preparation, hypothermia, and open cardiac surgery, but were given intravenous heparin at the onset of cooling. Ten dogs received 3 mg. of heparin per Kg. of body weight and 5 received 2 mg. per Kg. of body weight. No blood transfusions were given. Animals operated on were given 500 to 1,000 ml. of an electrolyte solution and those not subjected to surgery were given 500 ml.

Prothrombin utilization appeared to be adequate in all groups. No fibrinolysin was detected in any group. Hemoconcentration occurred in all groups undergoing cooling, despite fluid administration in excess of blood loss. In group A only minimal changes occurred in proaccelerin, proconvertin, prothrombin, and fibrinogen. A significant decrease in these values occurred with hypothermia and an even greater fall was observed with the addition of surgery. Depletion of these factors is believed to be due to intravascular clotting. Intravascular clotting predisposed to dangerous thromboembolic phenomena including several deaths in the hypothermia and surgery group that were believed to be due to pulmonary emboli. Hemorrhage after rewarming was a significant problem in the animals undergoing hypothermia and surgery. The hemorrhage was attributed to depletion of the blood of certain factors necessary for coagulation by the intravascular clotting. Following the intravenous administration of heparin in group D, the decrease in proaccelerin, proconvertin, prothrombin, and fibrinogen was less severe. In addition the transient drop in platelet count associated with intravascular clotting was inhibited by heparin. None of the animals in this group showed evidence of thromboembolic phenomenon and the mortality was greatly reduced. Furthermore, no hemorrhage occurred following re-warming.

BROTHERS

CONGENITAL ANOMALIES

Gyllensward, A., Lodin, H., Lundberg, A., and Moller, T.: Congenital, Multiple Peripheral Stenoses of the Pulmonary Artery. Pediatrics **19**: 399 (March), 1957.

This paper reports 7 cases of congenital malformation of the pulmonary artery in which not only valvular stenoses but also multiple sites of stenoses in the main pulmonary artery or its main branches were present. The physical findings in these cases, as well as the findings of catheterization and angiocardiography are presented. There are 2 main types of narrowing of the pulmonary artery or its branches. The first type is a simple one with narrowing immediately distal to the pulmonary valve. The second type consists of multiple (either short or long) narrowings extending along the main trunk to the branches. In the second type, valvular stenoses are usually present. These patients are physically undeveloped. They all have loud, protracted murmurs over the pulmonary region. At some sites it is continuous throughout the cardiac cycle. The second pulmonic sound is accentuated in all cases. There is right ventricular hypertrophy and right axis deviation. Pressure in the right ventricle and in the main pulmonary trunk is always raised. The possible embryologic development is discussed. Correction of the first type appears to be easy with excision of the membranous constriction, which creates a normal-sized lumen. Correction of the second type is difficult. Only the pulmonary stenoses can be re-

lieved here. There appears to be some familial incidence of these congenital stenoses.

HARVEY

Bender, F., Hilgenberg, F. and Jungehulsing, G.: Dextrocardia with Transposition of the Pulmonary Veins and Partial Agenesis of One Lung. Ztschr. Kreislaufforsch. 46: 172 (March), 1957.

In a 35-year-old woman origin of the right pulmonary veins from the right atrium and of the right superior lobe vein from the superior vena cava was disclosed by cardiac catheterization with dye injection. Partial agenesis of the right lung was considered as the cause of the dextrocardia. This was of the partial dextroversion type, since the P wave was upright in lead I and a deep Q was present in lead I.

LEPESCHKIN

Buhlmann, A., and Schaub, F.: Combination of High Intraventricular Septal Defect, Coarctation of Aorta, Persistent Ductus Botalli and Pulmonary Sclerosis. Ztschr. Kreislaufforsch. **46:** 181 (March), 1957.

The diagnosis was made in a 19-year-old woman by means of cardiac catheterization and blood gas analysis in the upper and lower extremities. The pulmonary artery pressure was 125/8 mm. of Hg and the electrocardiogram showed right ventricular hypertrophy with incomplete right bundle-branch block.

LEPESCHKIN

Samlert, H., and Oppel, K.: Arterial Oxygen Concentrations in Pulmonary Stenosis with Septal Defects, before and after Brock's Operation. Ztschr. Kreislaufforsch. **46:** 2 (Jan.), 1957.

In 8 patients with tetralogy of Fallot and 8 patients with Morgagni's syndrome (pulmonary stenosis) femoral arterial blood was studied at rest 1 to 3 weeks before and 4 to 10 weeks after dilatation of pulmonary stenosis. The decrease of the oxygen capacity after the operation was attributed partly to decreased shunting and partly to the bed rest required after the operation. The increase in the oxygen pressure found in 11 of the 16 patients was parallel to the increase in the work capacity, but the arterial oxygen deficit showed no relation to it. One patient showed at first an increase in the oxygen pressure and work capacity, but a decrease in both after 2½ years.

LEPESCHKIN

Rossi, E., and Probst, J.: Old and Recent Experiences in the Diagnosis of Interatrial Communications. Cardiologia **30:** 161 (March), 1957.

The authors discuss the diagnosis of atrial septal defect in infancy and childhood on the basis of an analysis of 32 unquestionable cases (selected from 120 in whom the diagnosis was suspected). A number of symptoms and signs considered as characteristic for this condition are inconstant in infants, in particular the pressure relationship in the different heart chambers. Characteristic, on the other hand, is an apical diastolic murmur. Right bundle-branch block in the electrocardiogram is typical only in adults probably due to progressive dilatation of the right ventricle. The most common roentgenologic signs in childhood are cardiomegaly, enlargement of the left middle segment, a hypoplastic aorta, and pulmonary vascular congestion. Right-sided cardiac catheterization provides direct evidence of the communication when the left atrium is entered and the size of the defect can be estimated by inflation of a balloon mounted to the catheter tip. To establish a left-to-right shunt an increase of at least 1.9 volumes per cent of the oxygen content in the right atrium must be postulated. The authors conclude that while in typical cases the diagnosis of an atrial septal defect can usually be made on the basis of physical and roentgenologic findings, atypical cases may require cardiac catheterization and selective angiocardiography.

PICK

Wild, J. B., Eckstein, J. W., Van Epps, E. F., and Culbertson, J. W.: Three Patients with Congenital Pulmonic Valvular Stenosis Surviving for More than Fifty-Seven Years. Medical Histories and Physiologic Data. Am. Heart J. **53:** 393 (March), 1957.

The clinical and physiologic observations on 3 patients, ages 69, 57, and 57, with congenital pulmonic valvular stenosis are presented. These observations, although not permitting broad generalizations, suggest that patients with this heart anomaly will probably be able to lead a reasonably active life until after middle age if the following conditions are found: a nearly normal minute volume cardiac output at rest, a right ventricular systolic pressure of 100 mg. Hg or less, a normal pulmonary artery pressure, and no symptoms referable to the heart defect.

SAGALL

CONGESTIVE HEART FAILURE

Gold, J., and Bellet, S.: Acetyldigitoxin in the Treatment of Heart Failure. New England J. Med. **256:** 536 (March), 1957.

The authors report their experience with acetyldigitoxin (Acylanid) in the treatment of 72 patients with varied etiologic types of heart

disease who had congestive heart failure, atrial fibrillation or flutter, or both, with a rapid ventricular rate. As with other digitalis preparations, individualization of the digitalizing and maintenance doses was found necessary for maximum therapeutic results and the avoidance of toxicity. In most cases adequate digitalization was obtained with 1.6 to 2.0 mg. of acetyldigitoxin given in 24 hours. The maintenance dose ranged from 0.125 to 0.33 mg. per day with most patients requiring 0.10 to 0.15 mg. daily. In some patients acetyldigitoxin was better tolerated and resulted in more adequate control than the various digitalis preparations previously used. In contrast to the authors' experience with digitoxin, acetyldigitoxin appeared to have the advantage of less frequent toxicity due to overdosage. When toxicity developed nausea and vomiting often were early symptoms. In most cases toxicity, when present, tended to disappear promptly in 1 to 3 days after withdrawal of the drug, but in 2 patients the toxic signs lasted for 8 and 14 days, respectively.

SAGALL

Race, G. A., Scheifley, C. H., and Edwards, J. E.: Hydothorax in Congestive Heart Failure. Am. J. Med. **22**: 83 (Jan.), 1957.

Two hundred and ninety cases of congestive heart failure with hydrothorax of at least 250 ml. were studied at autopsy. Twenty-four (8.3 per cent) had unilateral right sided and 11 (3.8 per cent) had unilateral left-sided hydrothorax, whereas in 255 patients (87.9 per cent) it was bilateral. The total incidence of right (279) and left (266) hydrothorax was almost equal. Fifty of 55 patients with atrial fibrillation had bilateral hydrothorax. Four of the 5 with unilateral hydrothorax had it on the left side.

KURLAND

CORONARY ARTERY DISEASE

Waaler, B. A.: The Effect of Permanent Anticoagulant Therapy on Symptoms and Mortality in Angina Pectoris. Acta med. scandinav. **157**: 289 (May 4), 1957.

Two hundred and seventy-five patients having angina pectoris attributed to coronary artery disease were treated with Dicumarol or phenylindanedione for periods averaging 2.5 years. The rationale was the prevention of coronary thrombosis and, possibly, the inhibition of coronary atherosclerosis. The desired degree of prothrombin-proconvertin (Owren) depression of 10 to 30 per cent of normal was obtained on the majority of tri-weekly checks in approximately half of the patients.

The mortality rate of 0.0496 during the first year of treatment was significantly lower than the rate of 0.1527 in a nonanticoagulated group. In the anticoagulated group, mortality was significantly less among those whose angina began within 1 year before starting treatment. Before anticoagulation the apparent myocardial infarction rate was 0.245 per year, which contrasted with a rate of 0.161 in the same group under treatment. The gradual and sustained improvement in effort tolerance in 50 per cent of patients suggested therapeutic effect beyond that of a placebo. The occurrence of clinical improvement, however, did not correlate with the intensity of anticoagulant effect. Important bleeding episodes, usually from the nose or urinary tract, were noted only once in every 20 treatment years while trifling hemorrhages occurred slightly more frequently.

ROGERS

Biörck, G., Blomqvist, G., and Sievers, J.: Cholesterol Values in Patients with Myocardial Infarction and in a Normal Control Group. Acta med. scandinav. **156**: 493 (Feb. 2), 1957.

The average total serum cholesterol levels of a group of patients hospitalized in Malmo, Sweden, for acute myocardial infarction were compared with those of healthy men from the same area and with those of healthy men from Minnesota. Of the men aged 40 to 49 years, the cholesterol levels averaged 300 mg. per cent and were significantly higher than those of the controls, which averaged 220-235 mg. per cent. The older male patients and controls had similar levels in the latter range. Female patients aged 50 to 79 years had levels averaging 60 mg. per cent higher than those of males of the same age. It was suggested that the younger coronary patients may derive from a somewhat different population than older patients.

ROGERS

Dreyfuss, F., Toor, M., Agmon, J., and Zlotnick, A.: Observations on Myocardial Infarction in Israel. Cardiologia **30**: 387 (June), 1957.

One thousand twenty cases of acute myocardial infarction observed in 2 Israeli hospitals over a period of 11 and 14 years were analyzed with regard to age distribution, sex ratio, and the incidence of hypertension, diabetes, and hypercholesteremia. There was a distinct difference in the distribution among the various Jewish ethnic groups, with prevalence in European-born Jews and rarely occurring in Oriental Jews, except when the latter had lived for some time under western conditions (and diets). The number of individuals revealing hypercholesteremia corresponded to figures found in other studies made

on predominantly Jewish populations. However, the incidence of hypertension and diabetes was comparatively low. The death rate amounted to 23.6 per cent (21.9 per cent for men, and 30.5 per cent for women). It was definitely lower (12.8 per cent) in patients treated with anticoagulants.

PICK

Nesvadba, P., and Chlumsky, J.: Contribution to the Inflammatory Alterations of the Coronary Vessels. Cardiologia **30**: 376 (June), 1957.

Autopsy findings are reported of a 38-year-old woman with a history of myocardial infarction, heart failure, and an apical ventricular aneurysm. Histologic studies disclosed a tuberculous endarteritis of the descending branch of the left coronary artery with narrowing of the lumen by tuberculous nodules containing giant cells. The etiology, pathology, and clinical features of inflammatory lesions of the coronary vessels are reviewed and discussed.

PICK

Forster, G., and Weissmann, C.: The Glutaminate-Oxalacetic Transaminase Activity of the Serum in Cardiac Infarction. Cardiologia **30**: 196 (March), 1957.

The authors report their experience with serum transaminase determinations in 130 patients. Eighty normal individuals revealed values varying between 7 and 43. In 20 patients with typical myocardial infarcts, the serum transaminase became elevated within 20 to 48 hours to degrees approximately proportional to the extent of the infarction. Three to 7 days after the infarction the values returned to normal levels. Among 12 patients classified as coronary insufficiency, the test was negative 10 times. Protracted transaminase elevation was caused by extracardiac factors such as embolism and gangrene of an extremity or parenchymatous liver disease, such as hepatitis, cholangitis, liver metastasis, and mushroom poisoning. It is concluded that serum transaminase determinations are valuable in the early diagnosis of clinically and electrocardiographically atypical cases of myocardial infarction. A repeatedly negative test rules against such a diagnosis.

PICK

Berne, R. M., Blackmon, J. R., and Gardner, T. H.: Hypoxemia and Coronary Blood Flow. J. Clin. Invest. **36**: 1101 (July), 1957.

These experiments were performed to differentiate the effects of low arterial oxygen tension and that of myocardial hypoxia on coronary vessels. If the supply of oxygen to the myocardium was maintained the oxygen content of coronary perfusates had no direct effect on coronary resistance. However, when coronary sinus blood fell below the normal 5.5 volumes per cent, coronary blood flow increased no matter what the arterial oxygen content was observed to be. Since venous oxygen reflects myocardial oxygen, it is possible to ascribe hypoxic coronary dilation to low myocardial oxygen content. When arterial oxygen content was reduced but myocardial oxygen was not lowered there was no increase in coronary flow.

OPPENHEIMER

Egorov, P. I., and Ostapiuk, F. E.: Results of Cardio-Omentopexy in Coronary Insufficiency. Klin. Med. **35**: 45 (Jan.), 1957.

Nineteen patients with intractable coronary insufficiency underwent cardio-omentopexy. Eight lost their anginal attacks immediately after the operation, 2 showed moderate improvement, 4 became worse, and 5 died soon after the operation because of myocardial infarction, or intestinal paresis, or both. The best results were achieved in persons under 60, without disturbances of fat metabolism, cardiac failure, or extensive electrocardiographic changes. The disappearance of complaints immediately after the operation, while the electrocardiogram in some cases showed appearance of fresh infarction, can be explained only by interruption of sensory nervous pathways. In some patients similar improvement resulted from novocaine infiltration of the anterior mediastinum.

LEPESCHKIN

Bolt, W., Balodimos, J., Kann, J., Valentin, H., and Venrath, H.: Determination of Physical Work Capacity of Patients with Old Myocardial Infarction. Ztschr. Kreislaufforsch. **46**: 284 (April), 1957.

In 58 patients who had acute myocardial infarction 1 to 5 years previously, and who had no signs of heart failure at rest and no arryhthmias, the oxygen consumption during work on an ergometer was registered continuously by means of a closed-circuit spirometer filled with oxygen. The exercise was started at 20-30 watts and increased 10-30 watts every minute until the oxygen consumption became constant or until pain, palpitation, fatigue or dyspnea appeared. More than one third of these patients had a maximal oxygen consumption still within normal limits for the age as determined on 500 normal persons. The decrease in cardiac reserve was in general proportional to the extension of the infarct as determined electrocardiographically in the acute phase, but often showed considerable discrepancy with the electrocardiogram at the time of the test. The determination of the cardiac re-

serve by this method was of great importance in the decision for or against resumption of normal activity.

LEPESCHKIN

Honey, G. E., and Truelove, S. C.: Prognostic Factors in Myocardial Infarction. Lancet 1: 1155 (June 8), 1957.

The histories of 543 cases of acute myocardial infarction admitted to a general hospital were reviewed in order to evaluate the influence of anticoagulants and other factors affecting the prognosis. In the acute attack the mortality rate was 34.9 per cent. One third of these deaths occurred on the first day. The following were not found to influence the prognosis: history of a previous attack, previous angina pectoris, preexisting hypertension, dyspnea on exertion, onset at effort or rest. The risk of death within the first 48 hours was enhanced by the presence of shock or hypotension. Among patients who survived the first 48 hours, the following factors were associated with an increased mortality rate during the acute episode: history of cardiac asthma, congestive heart failure, arrhythmias (including extrasystoles), gross cardiac enlargement, and diabetes mellitus. The over-all influence of anticoagulant therapy on the mortality rate was not considered great. The only substantial effect was a striking reduction in the number of deaths from pulmonary embolism.

KURLAND

ELECTROCARDIOGRAPHY, VECTORCARDIOGRAPHY, BALLISTOCARDIOGRAPHY, AND OTHER GRAPHIC TECHNICS

Sachs, D.: Comparative Esophageal and Precordial Phonocardiography in Humans. Arch. Kreislaufforsch. 25: 198 (Jan.), 1957.

In 42 normal persons and 58 cardiac patients esophageal phonocardiograms were registered through a 70-cm.-long stomach tube, having an internal diameter of 3.5 mm. and a lateral opening 15 mm. long, covered with a fine rubber membrane. Shorter tubes showed disturbing undamped vibrations in the low frequency range (35 c.p.s.). In all persons the atrial sounds had an amplitude on the average 4 times greater in esophageal registration than in precordial registration, and were registered often also in the 140- and 250-c.p.s. frequency ranges even in normal persons. In aortic valvular disease the diastolic and especially the presystolic murmurs were much louder in esophageal positions, while the systolic murmurs showed higher amplitude in precordial positions. In mitral disease the systolic murmurs were louder in the esophageal positions, whereas the diastolic and presystolic murmurs were louder in the precordial positions. In congenital heart disease esophageal positions yielded higher amplitudes, especially in the case of systolic murmurs of atrial septal defects. In hypertension presystolic murmurs were more common in the esophageal positions. In asthma and pulmonary emphysema all acoustic phenomena were considerably louder in the esophageal position, and in 1 patient the systolic murmur of mitral insufficiency could be registered only in the esophagus.

LEPESCHKIN

Fleisch, A. O., Schaub, F., and Buhlmann, A.: Phonocardiographic Findings in Atrial Septal Defect. Ztschr. Kreislaufforsch. 46: 62 (Jan.), 1957.

Of 15 adult patients with atrial septal defects in whom the diagnosis of atrial septal defect was made by cardiac catheterization, 12 showed an abnormally loud atrial sound having a frequency of 70 to 250 c.p.s.; the intensity seemed to depend on the degree of pulmonary hypertension. Twelve patients showed a split or widened first sound, and 11 of these had right bundle-branch block. All had a systolic murmur with a maximum at 70 c.p.s., not due to tricuspid insufficiency. Reduplication of the second sound was found in 11 cases; it had no relation to the width of the QRS complex, and was attributed to increased pulmonary flow in addition to right bundle-branch block. A decrescendo diastolic murmur, maximum in the pulmonic region, beginning immediately after the second sound and having a frequency of 35 to 140 c.p.s., was found in 10 cases; it was not attributed to pulmonary regurgitation, as it was not accompanied by a low diastolic pulmonary artery pressure.

LEPESCHKIN

Stallmann, F.: On the Theory of Electrocardiographic Leads. Arch. Kreislaufforsch. 25: 291 (Feb.), 1957.

On the basis of the reciprocity theory of Helmholtz, a dipole in the heart produces a deflection in a given lead that is equal to the projection of its vectors on the lead vector, multiplied by the lead magnitude; these values can be determined by applying an external current to the lead. If the location of the cardiac dipole vector is known, its magnitude and direction can be determined from 3 bipolar leads. The use of unipolar leads would not supply any additional information; this can be expected only from leads directly from the surface and cavities of the heart. The right and left ventricular components of the cardiac vector can be determined by ar-

ranging multiple leads so that, when external current is applied to them, no current will flow in 1 ventricle (compensatory "stagnation leads"); the cardiac vector in these leads will correspond to the vectorial component of the other ventricle.

LEPESCHKIN

Dohrmann, R., and Schmitt, W.: The Influence of Hypertension on the Vectorcardiogram with Special Reference to the Ventricular Gradient. Arch. Kreislaufforsch. **25**: 255 (Feb.), 1957.

The ventricular gradient and the area vector of QRS in the frontal plane were determined in 294 persons with hypertension and in 36 persons with normal blood pressure. It was found that in persons with long-lasting hypertension the gradient showed a progressive decrease with increasing mean arterial pressures from a pressure of 130 mm. on, while the QRS vector and the roentgenologic heart size showed a progressive increase. However, the range of variability was considerable. A tendency to left axis deviation of QRS appeared at higher pressure levels, but the scatter was very great. The best correlation with the mean pressure was shown by the ratio of the gradient to the QRS vector.

LEPESCHKIN

Hilmer, W., Moll, A., and Northoff, F.: Hypertrophy of the Venous Ventricle in Dextrocardia. Arch. Kreislaufforsch. **25**: 275 (Feb.), 1957.

Simple dextroposition of the heart (without rotation) does not affect the limb leads of the electrocardiogram or causes only a vertical QRS axis. Hypertrophy of the venous ventricle in this case causes right axis deviation as in normal heart position. In mirror-image dextrocardia it causes left axis deviation as in the left ventricular hypertrophy pattern, but P waves are inverted in lead I. Nodal rhythm in such cases is characterized by inverted P waves in leads I through III. Incomplete dextroversion (rotation to the right) is characterized by left axis deviation with inverted T waves in aV_L and sometimes even in lead I. Complete dextroversion is accompanied by transposition of the great vessels, and the venous ventricle has a posterior position. Hypertrophy of this ventricle in the illustrated case caused W-shaped QRS complexes with deep Q waves in leads I-II, while lead I showed an upright P and a deeply inverted T wave. This corresponds to the general rule that hypertrophy of the arterial ventricle causes accentuation of the normally present axis deviation, while hypertrophy of the venous ventricle causes reversal of this deviation.

LEPESCHKIN

Rosa, L., and Kunos, I.: Phonocardiographic and Stethographic Studies in Persistent Ductus Arteriosus Botalli. Ztschr. Kreislaufforsch. **46**: 161 (March), 1957.

Study of 23 cases of operated persistent ductus arteriosus shows that the systolic-diastolic murmur appears at the beginning of ventricular ejection and shows a maximum during rapid ejection, another maximum at the time of peripheral reflection of the aortic wave, as shown by the K wave of the ballistocardiogram, and sometimes a third maximum during the third or fifth heart sound. The murmur shows a sharp minimum at the time of opening of the A-V valves. The maxima are distinct also in phonocardiograms taken over the abdominal aorta, and are attributed to variations in the aortic and pulmonary pressures.

LEPESCHKIN

Herold, G., and Kaindl, F.: Direct Electrocardiographic Leads in Right Ventricular Hypertrophy. Ztschr. Kreislaufforsch. **46**: 57 (Jan.), 1957.

In 21 patients undergoing cardiac operations 4 leads from the ventricular surface to the central terminal were taken by means of a disk 7 mm. in diameter, covered with gauze saturated with saline. In 4 patients with persistent ductus arteriosus an RS complex was registered at the base of the right ventricle, rS at the apex of the right ventricle and the base of the left, and qRs at the apex of the left ventricle. In acquired mitral stenosis R was sometimes taller in the right apical lead and S deeper in the left apical lead, but otherwise the pattern was the same as in persistent ductus arteriosus. All cases with congenital heart disease leading to marked right ventricular hypertrophy had tall R waves, sometimes without S waves, on the right ventricular apex, while deep S waves were present on the left ventricular apex. There was no difference between right ventricular pressures in acquired and congenital right ventricular hypertrophy, and the more pronounced electrocardiographic signs in the latter were attributed to a longer period of development of hypertrophy.

LEPESCHKIN

Dittrich, W.: The Amplitude of the Heart Sounds in Mitral Stenosis. Ztschr. Kreislaufforsch. **46**: 15 (Jan.), 1957.

In 53 patients with mitral stenosis the phonocardiogram from the midprecordial region was registered with a frequency range above 250 c.p.s. The absolute amplitude of the heart sound varied up to 113 per cent; this variability was greatest for the first heart sound in atrial fibrillation and for the second component of the reduplicated second sound in sinus rhythm. The average am-

olitude of this component in relation to that of he second sound was 0.4, while that of the first ound was 1.1. Decrease in the heart rate was sually accompanied by increase in the amplitude of this component, while the first sound became smaller; at extremely low rates the first ound again became louder. After mitral commissurotomy, in anxiety, on deep inspiration, or fter passive elevation of the legs the second omponent usually became softer, while the second sound itself became louder. Mild exercise or leterioration of the cardiac condition caused the opposite changes.

LEPESCHKIN

Reeves, T. J., Ellison, H., Eddleman, E. E., Jr., and Spear, A. F.: The Application of Direct Body Ballistocardiography to Force Ballistocardiography. J. Lab. & Clin. Med. 49: 545 (Apr.), 1957.

It was demonstrated that acceleration ballistocardiograms from aperiodic or very low-frequency ballistocardiograms are similar, in young normal subjects, to the displacement ballistocardiogram from a direct-body technic altered so as to increase body frequency and the degree of damping of the system. The resonant frequencies and ratios of damping of young normal subjects were determined for an unmodified direct-body technic and for the putty-bed technic. The effect of the putty bed and packing was to increase the resonant frequency and damping coefficient in all subjects. Frequency-response curves for amplitude and phase relationship were plotted from the data obtained, for an undamped direct-body method, and for the putty bed modification of the direct-body technics. When these curves were compared to the frequency-response curves of acceleration of a low-frequency system, the reasons for similarity of ballistocardiograms from the 2 systems through a limited range of forcing frequencies became apparent. It was shown that the velocity and acceleration traces from an ideal high-frequency ballistocardiogram would be proportional to the third and fourth derivatives of the displacement of the circulatory mass, or to the first and second derivatives of the acceleration or force of the circulatory mass. Potential application of such derivations was briefly discussed.

MAXWELL

Scherf, D., Schott, A., Reid, E. C., and Chamsai, D. G.: Intermittent Parasystole. Cardiologia 30: 17 (Apr.), 1957.

A case is described with ectopic premature beats that at times were interpolated. Their coupling varied, usually with progressive increments until 1 premature beat was dropped and this in a repetitive fashion. At other times, there was a periodic increase followed by decrease in the length of the coupling. The authors interpret this unusual arrhythmia as an intermittent type of parasystole, assuming a pacemaker with irregular discharge, the latter occurring spontaneously or as a consequence of carotid sinus pressure. In support of their view that arrhythmias of this type are caused by a primary disorder of impulse formation rather than of impulse conduction an additional case with similar features is described.

PICK

Fleisch, A. O., and Schaub, F.: The Clinical Significance of Electrocardiographic Alterations of the Postextrasystolic Sinus Beat. Cardiologia 30: 236, (Apr.), 1957.

Among 600 electrocardiograms with premature systoles, 33 showed an anomaly of the first subsequent sinus beat consisting in T inversion, S-T depression, or a negative U wave. These occurred after supraventricular as well as ventricular premature beats and regardless of whether the ectopic beat was interpolated or led to a compensatory pause. In 14 cases this transient T-wave alteration was the only abnormality of the electrocardiogram, but in 28 cases some cardiac pathology (hypertension, coronary disease, valvular lesions, or myocarditis) could be established on clinical grounds, and in the remaining 5 it appeared very likely. On the basis of their material, the authors arrived at no conclusion as to the exact mechanism of the anomaly.

PICK

Holzmann, M.: The Differential Diagnosis of Ventricular Tachycardias. Cardiologia 30: 204 (March), 1957.

The difficulties in the diagnosis of the ventricular origin of a paroxysmal tachycardia are illustrated in 4 patients. In the first 2 patients, the diagnosis of a ventricular tachycardia was made on the basis of incomplete A-V dissociation with ventricular captures and fusion beats, although in the first, the intermittent occurrence of retrograde conduction suggested a supraventricular origin. In the third patient, an instance of atrial flutter, a ventricular tachycardia was transiently imitated by aberrant ventricular conduction developing when the atrial rate was slowed, and a 1:1 ventricular response was induced, by the administration of quinidine. The last patient demonstrated that the problem of differentiating an A-V nodal tachycardia with bundle-branch block from a ventricular tachycardia cannot always be resolved even with the use of esophageal leads. In this instance, in order to locate the origin of the ectopic rhythm

to the A-V node, 2 assumptions were necessary: a bilateral ventricular conduction defect of different degree and a Wenckebach phenomenon of retrograde conduction.

PICK

Ferrero, C., Leupin, A., Moret, P. and Cuénod, C. L.: Evaluation of Arterial Disease of the Lower Extremities by Volumetric Sphygmography. Cardiologia **30**: 126 (Feb.), 1957.

The authors applied a combined oscillo-pneumographic method to study the effect of exercise in normal individuals and in patients with severe hypertension, coronary disease, diabetes, and obliterating endarteritis. In normal individuals effort produced a characteristic deformation of the resting volumetric curve with lowering of the dicrotic wave. In disorders of the arterial circulation of the legs, the resting sphygmic deflections were smaller and delayed, the duration of the deformation after exercise was prolonged and no dicrotic waves were registered. On the basis of their experience in 23 patients suspected clinically to have a vascular disorder of the lower extremities, the authors believed that volumetric sphygmography permitted the detection of arterial disease in an early stage.

PICK

Wierum, C., and Glenn, F.: Electrocardiographic Indications of Significant Mitral Insufficiency in Patients with Mitral Valve Disease. Am. Heart J. **53**: 359 (March), 1957.

Study of 122 patients who underwent cardiotomy for mitral commissurotomy revealed a group of patients with a predisposition to left ventricular hypertrophy because of significant mitral insufficiency, hypertension, or aortic disease. From this series electrocardiographic criteria were derived which, in many instances, accurately selected the patients in this group from the others, pointing out that if these criteria are found in a patient without hypertension or aortic disease they constitute a strong indication of significant mitral insufficiency. These criteria are as follows: (a) $Sv_1 \geqq 10$, (b) $Sv_2 \geqq 26$, (c) $Rv_6 \geqq 15$, and (d) Sv_1 or v_2+Rv_5 or $v_6=34$. In the presence of atrial fibrillation these criteria were entirely specific in this series, but were unsatisfactory when applied to cases with a normal rhythm, because they yielded a high number of false-positive results.

SAGALL

ENDOCARDITIS, MYOCARDITIS, AND PERICARDITIS

Tesluk, H.: Giant Cell versus Granulomatous Myocarditis. Am. J. Clin. Path. **26**: 1326 (Nov.), 1956.

The autopsy, in a 22-year-old white man who had been admitted to the hospital in coma and shock and who died approximately 1 hour after admission, demonstrated the presence of numerous pale yellow patchy foci scattered throughout the myocardium ranging up to 2 cm. in their greatest dimension. These foci were more conspicuous in the left ventricle and in the interventricular septum. Microscopic study of these foci demonstrated the presence of an extensive inflammatory process in the myocardium, characterized by cellular infiltration consisting predominantly of lymphocytes and eosinophils with moderate numbers of macrophages and plasma cells. In addition, large numbers of multinucleated cells were present and several of these seemed to represent transitional forms from muscle fibers. These myogenic giant cells contained from 2 to 15 nuclei and had pale cytoplasms that were somewhat vacuolated. Ephithelioid cells and "true" inflammatory giant cells of the type associated with granulomatous inflammations were not observed. Blocks of tissue from the myocardium were studied with tissue culture technics but these failed to demonstrate cytopathogenic activity. On the basis of the pathologic findings at autopsy, the case properly should be classified as one of giant-cell myocarditis and should be distinguished from cases of granulomatous myocarditis. There may be a relationship between the 2 but it is not altogether a clearly established one. It is therefore suggested that the term giant-cell myocarditis should be used to designate those cases characterized by the presence of multinucleated fibers in the myocardium. Giant-cell myocarditis probably represents a type of inflammatory response to invasion of the myocardium by a virus, although it is recognized that in rare instances, this type of inflammatory response can be caused by specific bacterial or toxic agents. The term "giant-cell myocarditis" is a useful one in designating the particular lesion under discussion and can be used to separate this particular entity from the larger category of instances of interstitial myocarditis of obscure cause.

WENDKOS

Fabor, V., and Fischer, S.: Acute Idiopathic Myocarditis. Acta med. scandinav. **154**: 135 (fasc. II), **1956.**

An instance of acute idiopathic myocarditis occurring in a woman aged 35 years is described in detail. The major symptoms were malaise, fever, pain in the chest, dyspnea, pallor, and sweating. There was orthopnea, cyanosis, and pleural effusion. The electrocardiograms showed low voltage in the standard leads and a monophasic negative complex in lead CF_2. Treatment with ACTH, 20 mg. 3 times daily, and cortisone 200 mg. 3 times daily for 5 days prior to her death caused a transitory improvement but did not alter her downward course, owing to cardiac

insufficiency. The myocardium showed mottled yellow areas of necrosis with hyperemic portions and interstitial hemorrhage. The most severe changes were in the wall of the left ventricle. The microscopic studies showed widespread myocardial inflammatory infiltration with lymphocytes and plasma cells and dispersed longitudinal fibrils in some muscle fibers and others completely destroyed with hyalinization. There was some proliferation of the sarcoplasm nuclei in zones between normal and inflammatory muscle fibers and, in addition, spindle-shaped fragments. These muscular giant cells showed a coarse, granular sarcoplasm with striation. The patient had no demonstrable infection. There was no primary vascular change.

ROSENBAUM

Bayer, O., Grosse-Brockhoff, F., Loogen, F., and Wolter, H. H.: Hemodynamic Repercussions of Constrictive Pericarditis on the Pulmonary and Systemic Circulation. Ztschr. Kreislaufforsch. **45**: 697 (Sept.), 1956.

The right ventricular pressure curve in 24 patients with constrictive pericarditis showed a sudden early diastolic dip, reaching almost to the 0-line followed by a positive overshoot and subsequent horizontal plateau; in patients with atrial fibrillation the pressure during this plateau was identical in the atrium and ventricle; this indicated that almost the entire ventricular filling took place during the dip. The loud third heart sound occurred at the nadir of this dip, 0.08 to 0.11 second after the second sound; it was attributed to sudden stoppage of ventricular inflow due to resistance of the constricting tissue. Its great loudness in some cases could have been due to temporary closure of the mitral valve at that time. The pulmonary arterial pressure curve showed a nearly horizontal diastolic segment, which corresponded to the diastolic plateau of the left ventricular pressure curve and indicated that there was little or no late diastolic blood flow into the left ventricle. The characteristic configuration of cardiac pressure curves may allow the diagnosis of constrictive pericarditis even in the absence of characteristic clinical or roentgenologic findings.

LEPESCHKIN

HYPERTENSION

van 't Hoff, W.: Total Adrenalectomy for Malignant Hypertension. Quart. J. Med. **26**: 149 (Jan.), 1957.

Five patients with malignant hypertension and good renal function were treated by total adrenalectomy. Papilledema improved in all cases but in none was there a significant reduction in blood pressure nor evidence of prolongation of life. Attempts to reduce blood pressure further by reduction of maintenance cortisone or salt resulted in hypoadrenalism.

KURLAND

Fregly, M. J.: Effect of Renal Hypertension on the Preference Threshold of Rats for Sodium Chloride. Am. J. Physiol. **187**: 288 (Nov.), 1956.

Two bottles of fluid were made available to each rat. Distilled water was placed in one and salt solution in the other. Fourteen concentrations were used and changed every fourth day. The "preference threshold" for both control and hypertensive rats was .008 to .016 M. At all concentrations above threshold control rats preferred salt to water. In the case of hypertensive rats the preference was observed only from .016 to .090 M. Relative salt aversion was noted in hypertensive rats for salt solutions above .090 M. Salt aversion was not due to a difference in acuity in differentiating salt solutions and water. Aversion depended partly on concentration. The threshold for aversion was 5 times that of preference.

OPPENHEIMER

Fregly, M. J., and Cook, C. S.: Effects of Experimental Hypertension and of Aging on the Spontaneous Running Activity of Rats. Am. J. Physiol. **187**: 293 (Nov.), 1956.

Hypertension due to renal encapsulation was accompanied by increased activity of rats while the blood pressure was increasing. Temperature and light were controlled. After pressure was maximal, activity returned to control values. Normotensives and controls decreased equally with age.

OPPENHEIMER

Keller, R.: Experimental Investigations on the Hypotensive Action of Heparin. Arch. Int. Pharmacodyn. **110**: 300 (April), 1957.

In a previous study the author described changes of the hypotensive effect of 1 dose of heparin on rats pretreated with desoxycorticosterone acetate (DOCA) following damage of the mast cells. As compared to the normal hypertensive animal, the hypotensive effect of heparin was much more temporary. In the present study the author investigated the effect of the prolonged administration of heparin on the hypertensive rat after destruction of the intraperitoneal mast cells. The administration of 100 international units of heparin subcutaneously, 3 times a week, caused a lasting reduction of the blood pressure to roughly normal levels in DOCA-induced hypertension. A similar reduction of blood pressure was seen after intraperitoneal infusion of Tyrode solution, which left the mast

cells intact. Following the intraperitoneal injection of water, which damaged the mast cells, the hypotensive effect caused by heparin was transitory and persisted so for the 2-week period during which heparin was given. After intraperitoneal injection of 20, 50, or 80 mg. of histamine liberator 48/80, the reduction in the blood pressure caused by heparin was delayed compared to the untreated animal. After treatment with these small doses of histamine liberator only a relative small proportion of the granules of the intraabdominal mast cells were free. The author concludes that the presence of intraabdominal mast cells is essential for obtaining persistent reduction of blood pressure by heparin.

SCHERF

Barath, E., and Tarjan, R.: A New Medical Treatment of Hypertensive Diseases. Cardiologia **30**: 253 (Apr.), 1957.

On the basis of their experience in 407 patients, the authors recommend the combination of modern antihypertensive drugs with intravenous injections of 10 per cent sodium iodine to be administered once or twice daily in doses from 6 to 10 ml. The combination of reserpine with iodine proved particularly effective in ambulatory patients and led to long-standing improvement. The use of iodine is safe in elderly patients, but is contraindicated in the presence of hyperthyroidism or in pronounced tachycardia.

PICK

Gaunt, R., Ulsamer, G. J., and Chart, J. J.: Aldosterone and Hypertension. Arch. Int. Pharmacodyn. **110**: 114 (March), 1957.

Hypertension seems to be the usual component of the syndrome of primary aldosteronism. The results of animal experiments are contradictory. The authors gave 0.5 mg. of aldosterone subcutaneously in 0.05 ml. of purified sesame oil to 10 normal female rats 6 days per week for 7 months. Ten untreated animals served as controls. Blood pressures were taken at approximately 2-week intervals with a photo-electric tensometer. This treatment failed to produce signs of hypertensive disease or associated pathologic changes. The results of others were analyzed and no logical explanation could be offered for the differences.

SCHERF

METABOLIC EFFECTS ON CIRCULATION

Schaus, R.: The Ascorbic Acid Content of Human Pituitary, Cerebral Cortex, Heart, and Skeletal Muscle and Its Relation to Age. Am. J. Clin. Nutrition **5**: 39 (Jan.-Feb.), 1957.

A study of the total ascorbic acid concentration of samples of pituitary gland, cerebral cortex, myocardium, and pectoral muscle derived from individuals ranging in age from 7 days to 88 years revealed a statistically significant decrease of ascorbic acid concentration with age in the pituitary gland and the cerebral cortex. However, after an initial fall, no further decrease with age was found in the ascorbic acid concentration in the myocardium after the second decade and in the pectoral muscle after the fourth decade.

SAGALL

Rapaport, E., Kuida, H., Dexter, L., Henneman, P. H., and Albright, F.: The Cardiac Output in Paget's Disease before and after Treatment with Cortisone. Am. J. Med. **22**: 252 (Feb.), 1957.

The cardiac output was determined by the indicator dilution method in 6 patients with extensive Paget's disease before and during treatment with large doses of cortisone. Cardiac output was elevated initially in all patients. High doses of cortisone for 3 to 9 days produced a pronounced fall to normal levels. Cortisone also lowered the serum alkaline phosphatase but had no consistent effect on oxygen consumption, large-vessel hematocrit levels, total blood volume, pulse pressure, or mean arterial pressure. A pronounced drop in pulse rate was observed in 3 of the 6 patients.

KURLAND

Shepard, T. H.: Carbonic Anhydrase Activity in Blood of Patients with Chronic Respiratory Disease. Am. J. M. Sc. **233**: 162 (Feb.), 1957.

The enzyme carbonic anhydrase present in red blood cells and many other tissues is related to the exchange of carbon dioxide. There is no significant increase in the red blood cell carbonic anhydrase activity of patients with chronic respiratory disease. There was no significant correlation of carbonic anhydrase with severity of disease or serum carbon dioxide combining power. The enzyme increases with age if the values are expressed as units per milliliter of red blood cells. The amount of enzyme per milliliter of red blood cells decreases with increase in the hematocrit value.

HARRIS

PHARMACOLOGY

Hermann, H.: Mechanisms of the Decrease and Reversal of the Hypertensive Effects of Adrenaline. Arch. Int. Pharmacodyn. **110**: 83 (March) 1957.

Dale postulated that the reversal of the hypertensive effect of epinephrine was due to a competitive action at the level of specific receptors between epinephrine and the inversing substance. This latter substance would tie up the vasoconstricting receptors thus leaving free only the vaso-

dilators. This question was reinvestigated because benzodioxane is hypotensive in the anesthetized, but hypertensive in the nonanesthetized animal, and because of the advantage of using dogs without a spinal cord to prevent any cerebrospinal action on the vasomotor phenomena. In such animals benzodioxane retains its reversal action. This is also true for tolazoline and yohimbine. Other substances have less effect. There are, therefore, degrees in the power of inversion. Substances that inverse best are those with the strongest vasoconstricting effect. The author tried to block the vasodilating receptors by using Dilatyl; following this the hypotension caused by small doses of epinephrine disappeared and was replaced by hypertension to an even higher degree than that caused by arterenol. Finally, if the hypotensive and hypertensive receptors were blocked no epinephrine effect was noted. Therefore, the cause of the reversal is due to blockage of the receptors and not to a change in the receptors or in their response.

SCHERF

Cavanaugh, M. W., and Cavanaugh, D. J.: Studies on the Pharmacology of Tissue Cultures. I. The Action of Quinidine on Cultures of Dissociated Chick Embryo Heart Cells. Arch. Int. Pharmacodyn. **110:** 43 (March), 1957.

Differentiated embryonic cells of chick atria and ventricles separated by trypsin digestion retain their histologic character when grown in plasma-embryo extract clots. These cells were treated with doses of quinidine from 0.025 to 2.5 $\times$ 10^{-5} mg. per 1,000 cells. The number of living cells, of pulsating cells and the pulsation rate of the individual cells were measured. In the doses employed the number of living cells was not significantly affected. Up to 10^{-4} mg. per 1,000 cells there were no appreciable changes cytologically. The number of pulsating cells diminished. The pulsation rate and the magnitude of the contraction lessened with quinidine. Also the rate of pulsation of cell aggregates diminished. Although quinidine inhibited pulsation of heart cells there were considerable individual variations in the response of cells in different experiments. This may be due to the fact that the preparations were obtained in different stages of embryonic development.

SCHERF

Friedman, S. M., Nakashima, M., and Friedman, C. L.: Separability of the Effects of Pitressin and Adrenaline on Blood Pressure and Electrolytes. Arch. Int. Pharmacodyn. **110:** 170 (April), 1957.

Previous studies of the authors showed that pitressin acted directly on the distribution of water, sodium, and potassium between cells and environment. Studies with epinephrine and histamine have demonstrated that these shifts of electrolyte and water are correlated with changes of blood pressure. A general theory has been formulated that peripheral vascular resistance depends on the "sodium transfer systems" that regulate sodium entrance and extrusion in vascular smooth muscle. The present studies show that although pitressin and epinephrine both produce similar shifts in electrolytes they do so through separate mechanisms. In adult bilaterally nephrectomized albino rats the movements of water, sodium, and potassium between cellular and extracellular compartments were studied. Previous treatment with dibenzyline blocked the rise of blood pressure produced by epinephrine and also the movement of electrolytes. Under the same circumstances the rise of blood pressure and the transfer of sodium and water produced by pitressin were not inhibited. The authors conclude that although pitressin and epinephrine both act on the "sodium transfer system" their specific effects are exerted on separate parts of that system.

SCHERF

Schneider, J. A., and Rinehart, R. K.: Analysis of the Cardiovascular Action of Ibogaine Hydrochloride. Arch. Int. Pharmacodyn. **110:** 92 (March), 1957.

The action of ibogaine, one of the main alkaloids of the roots of *Tabernanthe iboga*, a shrub indigenous in French equatorial Africa, exhibiting alerting and sleep combating effects was examined on dogs and cats. It was found to have a negative chronotropic and inotropic effect on the heart. Intravenous injection in anesthetized dogs produced a fall of blood pressure mainly caused by a reduction of cardiac output. In unanesthetized dogs a rise of blood pressure was seen and explained by a central stimulating component. Atropine did not prevent the blood pressure drop due to ibogaine in the anesthetized cat. Associated with the drop of blood pressure was a drop in heart rate and respiratory rate. The mode of action of the negative chronotropic and inotropic effect of ibogaine is not clear. It is questionable whether cholinesterase inhibition is responsible, since atropine does not prevent the effects.

SCHERF

Collier, H. D., Meyers, F. H., and Schmitt, G. H.: Hemodynamic Effects of Infusions of Epinephrine and Arterenol in Normal and Shocked Dogs. Am. J. Physiol. **189:** 224 (May), 1957.

By slow infusion levarterenol decreased or had no effect on cardiac output. By the same method epinephrine increased output. Rapid intravenous injections reported elsewhere did not yield the

same result. Changes in output correlated with peripheral resistance. It is suggested that the increase in resistance due to arterenol may modify the positive inotropic action observed in isolated hearts. Changes in circulating plasma volume and intrathoracic blood volume were proportional to cardiac output. Shock due to reduced output did not change the responses to epinephrine or norepinephrine.

OPPENHEIMER

Borst, H. G., Berglund, E., and McGregor, M.: The Effects of Pharmacologic Agents on the Pulmonary Circulation in the Dog. Studies on Epinephrine, Norepinephrine, 5-Hydroxy-Tryptamine, Acetylcholine, Histamine and Aminophylline. J. Clin. Invest. **36**: 669 (May), 1957.

The test object was a preparation in which redistribution of flow in one lung while the other served as a control, was used as a measure of changes in vascular activity. Epinephrine and norepinephrine had only minor hemodynamic effects on the blood flow via the lung, which could be shown to be independent of changes in the left atrium. Serotonin, by the same criteria, was a potent pulmonary vasoconstrictor in doses which in these experiments were not bronchoconstrictor. Acetylcholine and histamine increased the pressure difference between the alveolar and pleural surfaces of the lung. When this variable was controlled the pulmonary vasomotor activity of these 2 agents was insignificant. Aminophylline was either vasodilator or ineffective.

OPPENHEIMER

Schneider, K. W.: Studies on the Influence of Sympathomimetic Substances on Some Circulatory Values. Arch. Kreislaufforsch. **25**: 1 (Jan.), 1957.

One hundred and ninety-seven patients were studied and in 32 the heart output was determined by the dye-dilution method, while in 24 pulmonary artery pressure was registered directly. After intravenous injection of Effortil the blood volume showed at first a decrease, then after 10 to 25 minutes, an increase; the systolic pressure showed a considerable increase, the diastolic pressure a slight increase, and the pulmonary artery pressure rose. The heart output and the circulation velocity were increased. Veritol caused a greater rise of diastolic systemic and pulmonary arterial pressures, and a smaller decrease in circulation time than Effortil. The elevated blood volume and heart output usually had returned almost to normal by the time the blood pressure reached its maximum. Sympatol caused increase of blood volume and heart output only in higher doses; the systolic and diastolic as well as the pulmonary pressure increased slightly. Peripherin caused an increase of blood pressure similar to that caused by Effortil, followed later by increased blood volume. Norepinephrine caused a parallel rise of systolic and diastolic pressure, bradycardia, and increased circulation time.

LEPESCHKIN

Jelliffe, R. W., Wolf, C. R., Berne, R. M., and Eckstein, R. W.: Absence of Vasoactive and Cardiotropic Substances in Coronary Sinus Blood of Dogs. Circulation Research **5**: 382 (July), 1957.

Substances with coronary vasodilator or vasoconstrictor properties as well as those with inotropic or chronotropic effects on isolated frog hearts were sought in the coronary blood of dogs. The experiments failed to demonstrate such substances in the blood draining normal, hypoxic or overperfused dog hearts. Such materials, if present in the myocardium for its regulation, either do not enter coronary venous blood, are destroyed by the process of oxygenation, or are inactivated by the blood itself during the brief period required for bioassay.

AVIADO

Leveque, P. E.: Auricular Fibrillation by Acetylcholine Injection During Hypopotassemia. J. Pharmacol. & Exper. Therap. **120**: 38 (May), 1957.

The combination of glucose and insulin injected intravenously to anesthetized dogs lowered the serum potassium concentration to a greater degree than either agent alone. When the serum potassium concentration was depressed to about 80 per cent of the control value, atrial fibrillation and flutter were provoked by the intravenous administration of acetylcholine. The acetylcholine induced by flutter was perpetuated by an infusion of acetylcholine and was arrested by an infusion of 10 per cent potassium chloride solution. This is a verification of the observation by others that potassium has an important role in atrial arrhythmias.

AVIADO

Clark, M. L., and Hagans, J. A.: The Diuretic Activity of a New Pyrimidinedione Administered Orally to Nonedematous Adults. J. Lab. & Clin. Med. **49**: 395 (March), 1957.

Rolicton, a new pyrimidinedione, administered to 18 nonedematous subjects in dosages of 1.2 Gm. to 2.4 Gm. per day for 3 days per week, produced a significant diuresis manifested by increase in urine volume and loss of body weight compared to a control period and to a placebo. Its potency appeared comparable to that of Mictine, but it was singularly free of the undesirable

side effects (nausea, anorexia, abdominal cramps, and vomiting) that often limit the use of the latter drug. The maximum diuretic effect of Mictine and Rolicton was achieved on the first day. After withdrawal of the effective diuretic agent, "rebound phenomenon" was noted, characterized by diminished urine excretion and a gain in weight on the seventh day. The use of nonedematous or normal subjects for the evaluation of diuretic agents appears feasible. Should such results accurately reflect the therapeutic responses observed in edematous patients, the utilization of this more homogeneous group to evaluate the effectiveness of a new diuretic compound would then be justified and desirable.

MAXWELL

Hammond, J., and Whitaker, W.: Effects of Intravenous Digoxin in Uncontrolled Auricular Fibrillation. Brit. Heart J. **19**: 23 (Jan.), 1957.

This study was designed to investigate the effect of intravenous digoxin on renal function in 6 patients with congestive failure and in 7 who had never experienced failure, all of whom had uncontrolled atrial fibrillation. Digoxin produced a reduction in heart rate in all, a rise in systemic pressure in 8, a fall in right atrial pressure in 10, and a marked rise in cardiac output in 4 with failure and a slight rise in 3 without failure. Renal blood and plasma flow and glomerular filtration increased in 3 with failure, and renal blood and plasma flow increased in 2 without failure. The renal fraction of the cardiac output increased in 1 patient with failure and 1 without failure. An increase in urinary sodium and chloride occurred in 3 with failure and 6 without failure. These findings indicate that changes in renal blood and plasma flow and glomerular filtration rate closely paralleled the change in cardiac output. Increase in salt excretion also usually paralleled an improvement in renal function but in some instances digoxin may have exerted a direct effect upon tubular reabsorption of salt.

SOLOFF

PHYSIOLOGY

Parr, F.: On the Pathologic Physiology of the Orthostatic Circulatory Disturbances. Arch. Kreislaufforsch. **25**: 101 (Jan.), 1957.

In 122 patients the heart output (from the blood pressure and pulse wave velocity), the active blood volume (dye dilution method), the circulation time and the electrocardiogram were determined in the recumbent position, 10 minutes after passively assuming an upright position, and 30 minutes after sitting down. Sixty-four persons showed insufficient venous regulation (decreased blood volume and heart output, no change in mean arterial pressure), 1 person showed insufficient arterial regulation (decreased mean pressure and blood volume, no change in heart output), 24 persons showed a combination of these 2 disturbances, and 11 showed no disturbances. The circulation time remained practically unchanged. The decrease of circulating blood volume (caused by trapping in the lower limbs and splanchnic region) averaged 22 per cent in the standing, 10 per cent in the sitting position. These orthostatic changes showed no relation to the values at rest. Twenty-two persons showed orthostatic collapse, characterized by general vasodilatation, increased circulation time and greatly decreased arterial pressure and heart output, with the blood volume sometimes showing no change. These changes were more pronounced if collapse was accompanied by bradycardia (10 persons), but the electrocardiogram remained normal in these cases or showed nodal or ventricular escape rhythms. Changes of T waves and S-T segments appeared only when collapse was accompanied by tachycardia. Their incidence was in general parallel to the decrease in circulating blood volume; this applied also to the subjective symptoms. Orthostatic disturbances tended to appear in patients with infections, intestinal or hormonal disease, in younger leptosomic persons, and after prolonged bed rest. They could disappear after improvement of the basic disease.

LEPESCHKIN

Bondurant, S., Hickam, J. B., and Isley, J. K.: Pulmonary and Circulatory Effects of Acute Pulmonary Vascular Engorgement in Normal Subjects. J. Clin. Invest. **36**: 59 (Jan.), 1957.

Pressure was applied to the body surface in order to produce an acute central and pulmonary vascular engorgement of short duration. Aviator's G suits or submersion in water were used to produce the pressure. As a result central venous pressures were increased and compliance was reduced. If pressure was maintained for 2 minutes, central venous pressure and compliance returned toward control values. This return was blocked by the infusion of norepinephrine or immersion of an arm in ice water. In control experiments without suit inflation these same 2 agents (norepinephrine and cold) were observed to produce a rise in central venous pressure of small magnitude and a similar decrease in compliance. However, if the suit was inflated during norepinephrine infusion central venous pressure increases and compliance decreases were larger than in untreated subjects. Pretreatment with hexamethonium decreased the rise in central venous pressure as a result of

suit inflation, but compliance responses were unchanged. The authors suggest that compliance changes depend partly on engorgement of the pulmonary vessels. Peripheral venous tone plays some role in the engorgement.

OPPENHEIMER

Freis, E. D., Schnaper, H. W., and Lilienfield, L. S.: Rapid and Slow Components of the Circulation in the Human Forearm. J. Clin. Invest. **36**: 245 (Feb.), 1957.

Forearm circulation has a rapid and a slow component. Rapid flow predominates although the volumes of the 2 are equal. When forearm flow increases the rapid component becomes larger as its volume also increases. It is suggested that the site of biphasic flow is in small vessels, since flow in many interarteriolar, intercapillary, and intervenular anastomoses is sluggish.

OPPENHEIMER

Shadle, O. W., Ferguson, T. B., Sabiston, D. C., Jr., and Gregg, D. E.: The Hemodynamic Response to Lanatoside C of Dogs with Experimental Aortic-Caval Fistulas. J. Clin. Invest. **36**: 335 (Feb.), 1957.

Test objects were dogs with chronic aortic-caval fistulae. Control observations demonstrated a high end diastolic pressure in the left ventricle. Cardiac output, stroke volume, and work were increased. Pulmonary edema, edema of extremities, and ascites indicated heart failure. One to 14 months later rapid digitalization with Lanatoside C failed to alter cardiac performance during the next hour. Similar results were obtained even if measurements were made 4 days after the animal had been on a maintenance dose of digitoxin.

OPPENHEIMER

Greenberg, R., and Lambeth, C. B.: Failure to Show Supersensitivity to l-Epinephrine and l-Norepinephrine in the Chronic Denervated Heart in Unanesthetized Dogs. Am. J. Physiol. **188**: 375 (Feb.), 1957.

Test objects were unanesthetized dogs with chronically denervated hearts. Rapid injections of l-epinephrine produced bradycardia and hypotension in a few animals. If the same material was given by infusion these same results were observed much more frequently. L-norepinephrine always produced hypertension and tachycardia. L-norepinephrine had approximately twice as much chronotropic action as l-epinephrine. Increased sensitivity to either drug was absent in 3 out of 4 animals. The authors conclude that these experiments do not support either l-epinephrine or l-norepinephrine as the important mediator of the sympathetic system.

OPPENHEIMER

Nahas, G. G.: Heart Rate During Short Periods of Apnea in Curarized Dogs. Am. J. Physiol. **187**: 302 (Nov.), 1956.

"Apneic oxygenation" is defined as arrest of ventilation following partial denitrogenation. This period was characterized by bradycardia, systemic hypertension, fall in central venous pressure, increase in end expiratory carbon dioxide, and fall in arterial pH. Bilateral cervical vagotomy did not block these effects. The observations were the same even though moderate hypoxia was present. The author is of the opinion that respiratory acidosis plays a large role in the bradycardia.

OPPENHEIMER

Rodbard, S., Krause, S., Lowenthal, M., and Katz, L. N.: Acute Dynamic Effects of a Shunt between a Systemic Artery and the Left Atrium. Am. J. Physiol. **187**: 458 (Dec.), 1956.

The left subclavian artery was anastomosed to the left atrium in dogs. When the shunt was suddenly opened the ventricle dilated acutely and then fibrillated. The lungs became congested and edematous. If the shunt was opened gradually, acute failure was not observed. When the shunt was opened a decreased peripheral resistance lowered aortic pressure. Left atrial pressure was abruptly elevated. Pulmonary arterial pressure was unchanged. Flow by way of the shunt was increased by epinephrine, strophanthin, and asphyxia.

OPPENHEIMER

Ederstrom, H. E., Vergeer, T., Rohde, R. A., and Ahlness, P.: Quantitative Changes in Foot Blood Flow in Dog Following Sympathectomy and Motor Denervation. Am. J. Physiol. **187**: 461 (Dec.), 1956.

Unilateral lumbar sympathectomy produced an increased blood flow in the ipsilateral foot during the first 3 postoperative days. However, at a later time under anesthesia, flow was less than in controls. Vasodilator drugs by vein or artery augmented flow on the operated side. The normal, but not the operated side, became warmer under anesthesia. Chronic motor denervation produced similar results. The authors suggest that the blood vessels of the sympathectomized or denervated foot were contracted by a humoral substance that had less effect on innervated normal vessels.

OPPENHEIMER

Green, H. D., Howard, W. B., and Kenan, L. F.: Autonomic Control of Blood Flow in Hind Paw of the Dog. Am. J. Physiol. **187**: 469 (Dec.), 1956.

Blood flow was measured in the skeletal muscles of the hind paw of the dog. Intra-arterial epinephrine and norepinephrine were vasocon-

strictors. Isoproterenol and methacholine were weak vasodilators. Reactive hyperemia after ischemia was not observed. Stimulation of the sympathetic chain at S_1 produced vasoconstriction. Intra-arterial dibenzyline blocked all types of vasoconstriction. Vasodilation was unaffected. This vascular area contained strong innervated alpha constrictor receptors. There were only a few adrenergic and cholinergic vasodilators.

OPPENHEIMER

Caster, W. O., Armstrong, W. D., and Simonson, E.: Changes in the Cardiovascular System Following Total Body X-Irradiation. Am. J. Physiol. **188**: 169 (Jan.), 1957.

There were no histologic changes in rat heart muscle after single doses of x-ray (700 r.) or chronic doses of 100 or 200 r. per month for 7 months. Deoxyribonucleic acid and actomyosin concentrations were decreased during the first 10 days after 700 r. The heart and lungs were edematous. Peripheral venous pressure was increased. Progressive changes in the electrocardiogram were observed. There was also a change in the mechanical action of the heart. In the case of chronic irradiation changes in the electrocardiogram were similar to those observed acutely. Exposure to 700 r. increased plasma volume 30-50 per cent, 6-10 days after exposure.

OPPENHEIMER

Ring, G. C., Moss, W. G., Reiner, I., Partin, H., and Kurbatov, T.: Changes in Arterial Dilution Curves Associated with Blockage of Abdominal Aorta, Hypoxia and Hemorrhage. Am. J. Physiol. **187**: 283 (Nov.), 1956.

The dye T-1824 and red cells marked with P^{32} were injected into the pulmonary artery of dogs. The characteristics of arterial dilution curves after blocking the descending aorta, after hypoxia and after transfusion following hemorrhage were studied. After pulmonary pressure was raised by blocking the aorta, the figure for peak concentration time divided by appearance time (PTC/AT) was increased, the concentration of labels rose to three fourths of peak concentration more quickly and the figure for peak concentration divided by mean concentration (PC/MC) diminished. The results following hypoxia were variable. In only 1 out of 8 dogs studied were the changes similar to those described above. In 5, opposite changes were found; and in 2, the changes were mixed. Transfusion following hemorrhage resulted in changes that showed no regular pattern. The changes with blocking of the aorta were those that would be predicted if pulmonary shunts opened.

OPPENHEIMER

Reymond, C., Desbaillets, P., Baudraz, B., and Rivier, J. L.: Exercise Test and Cardiac Catheterization. Cardiologia **30**: 259 (Apr.), 1957.

Cardiac catheterization at rest and following exercise corresponding to 30 to 40 watts was performed in 11 persons with normal cardiovascular systems and in 8 patients with fibrotic pulmonary tuberculosis who had restricted respiratory function but no evidence of cardiac involvement on physical, electrocardiographic, and roentgenologic examination. In all these cases, the exercise test led to changes in cardiodynamics that were well within normal limits. On the other hand, the same working load led to an abnormal reaction in 14 patients with organic heart disease. Ten patients with mitral lesions responded with signs of increased overload of the pulmonary circulation while in 4 patients with left heart failure the pulmonary arterial pressure rose but the resistance in the pulmonary circulation diminished following exercise. The significance of these findings with respect to surgery in pulmonary and mitral disease is discussed.

PICK

RENAL AND ELECTROLYTE EFFECTS ON THE CIRCULATION

Floyer, M. A.: Role of the Kidney in Experimental Hypertension. Brit. M. Bull. **13**: 29 (Jan), 1957.

Evidence suggests that there is an early phase after renal artery constriction in the rabbit and in the dog in which a renal pressor substance, which may or may not be renin, elevates the blood pressure. However, in the dog, rat, and rabbit some extrarenal mechanism is probably responsible for maintaining the elevated blood pressure in the later stages of hypertension, since removal of the clamped kidney does not lower the blood pressure. Another hypothesis assumes that some mechanism exists outside the kidney that tends to raise blood pressure but that is normally held in check by the kidney; (the extrarenal pressor mechanism). Such a mechanism would explain a rise in blood pressure in normal animals after removal of both kidneys (renoprival hypertension). Renin might not maintain hypertension by its peripheral vasoconstrictor effect, but it might have a local effect on the kidney and inhibit the function concerned with maintaining normal blood pressure. This would explain why antirenin, by releasing the kidney from the effect of renin, produces a fall in blood pressure as though it were temporarily removing the renal artery constriction. It is also possible that the kidney by some metabolic function, maintains intracellular electrolyte concentration and that failure to perform this function results in a change in the intracellular electrolytes of the smooth muscle cells of arterioles, which leads to hypertension.

SIMON.

AMERICAN HEART ASSOCIATION, INC.

44 East 23rd Street, New York 10, N. Y.
Telephone Gramercy 7-9170

"DOCTORS, HEART ASSOCIATIONS AND UNITED FUNDS"

An appeal to the medical profession to help in maintaining the American Heart Association as a "free American institution" in the face of pressure tactics by United Funds to force voluntary health agencies to give up their independent fund raising campaigns has been made by Robert W. Wilkins, M.D. of Boston, President of the AHA. Dr. Wilkins' appeal was contained in an article entitled, "Doctors, Heart Associations and United Funds," which was distributed as an insert with the February issue of *Modern Concepts of Cardiovascular Disease.*

In his article, Dr. Wilkins states, "We regard federated plans of fund raising, especially for local charity causes, as fully worthy of support, provided they are truly voluntary and not forced on either the people or the participating agencies." However, he cautions that if United Funds are permitted to undermine the efforts of the voluntary health agencies, "research will dwindle and the conquest of disease inevitably will be delayed. The result will be the needless loss of hundreds of thousands of lives."

Dr. Wilkins points out to the medical profession that the Heart Association and other national voluntary health agencies "are telling *your* story to the public; they are protecting you from governmental domination on one side and from local dictatorship on the other. But most important, along with you they are leading the way towards the control of the major chronic diseases."

"The medical profession," Dr. Wilkins adds, "will help to preserve its own freedom in the future if it insists now, through its county, state and national organizations, that the ethical voluntary health agencies be freed of further coercion by United Funds. Individual doctors, who wish to interest themselves and their patients directly in the work of the Heart Association, will receive not only an enthusiastic welcome, but also the satisfaction of contributing in an important way to a volunteer group, whose sole purpose is to help all physicians in their fight against disability and death."

Reprints of Dr. Wilkins' article may be obtained on request from your local Heart Association or the AHA.

ABSTRACTS OF PAPERS AND EXHIBIT APPLICATIONS DUE JUNE 13 FOR AHA SESSIONS

Abstracts of papers for presentation at the annual Scientific Sessions of the American Heart Association to be held in San Francisco October 24-26 must be submitted on official forms provided by the Association before June 13, 1958. Applications may be obtained by writing to F. J. Lewy, M.D., Assistant Medical Director of the American Heart Association.

Papers intended for presentation must be based on original investigations in, or related to, the cardiovascular field. Abstracts must be limited to 250 words or less and should contain in summary form the results obtained and the conclusions reached. Applications will be screened by the Association's Committee on Scientific Sessions Program.

Applications for space for scientific exhibits should be filed with the Association through Dr. Lewy not later than June 13, 1958. Applications for commercial exhibits may be requested through Steven K. Herlitz, Inc., 280 Madison Avenue, New York 16, N. Y.

ABSTRACTS DEADLINE IS MAY 31 FOR ARTERIOSCLEROSIS SOCIETY

Abstracts of papers to be presented at the annual meeting of the American Society for the Study of Arteriosclerosis are to be submitted by May 31 in quadruplicate to Forrest Kendall, Ph.D., Goldwater Memorial Hospi-

al, Welfare Island 17, New York, N. Y. Abtracts should not exceed 300 words including he title of the paper and the name of the uthor.

The Society will hold its meeting simulaneously with the Annual Scientific Sessions f the American Heart Association in San rancisco, October 24-26. Several joint prorams are being planned at that time.

BOOKLETS FOR PATIENTS ON SODIUM RESTRICTED DIETS

Three new booklets prepared especially for adult heart patients placed on sodium-restricted diets by their physicians have been published by the American Heart Association. The booklets are available to physicians from local Heart Associations or the national AHA office, for distribution to their patients. They are also being made available to patients by local Heart Associations on a physician's prescription. Copies may also be obtained by nurses, nutritionists, dietitians and hospital and nursing home staffs.

The new booklets were prepared under the direction of a committee representing four agencies in addition to the American Heart Association. They are the U. S. Public Health Service, the American Dietetic Association, the Council on Foods and Nutrition of the American Medical Association, and the Nutrition Foundation. Each booklet is designed to help patients follow the physicians prescription for a different level of sodium restriction: strict, 500 mg.; moderate, 1,000 mg.; and mild. Within each booklet, there is a choice to be indicated by the physician, of three different calorie levels, 1,200 calories, 1,800 calories and unrestricted. Food lists enable the patient to vary his meals as he becomes familiar with his basic diet plan. Weight watching, meal planning and problems of the family cook are discussed and practical suggestions on eating out and shopping for food are given.

CARDIOVASCULAR RESEARCH TRAINING PROGRAM IN GEORGIA

A Postgraduate Cardiovascular Research and Training Program, sponsored jointly by the American Heart Association and the National Heart Institute of the U. S. Public Health Service, will be conducted beginning July 1 in the Departments of Physiology and Pharmacology, Medical College of Georgia, Augusta. Trainees will be appointed for a one-year period. A stipend of $3800 plus $350 for each dependent and certain other expenses will be provided to participants. Inquiries and requests for application forms may be addressed to either of the directors of the program, W. F. Hamilton, M.D., or R. P. Ahlquist, M.D., Medical College of Georgia.

NEW CARDIOLOGY FOUNDATION

The International Society of Cardiology Foundation has been established in Chicago to support cardiovascular research throughout the world. Requests for such support may be addressed either to members of the Foundation's Board of Directors or Advisory Committee, or to Louis Katz, M.D., at the Foundation's Chicago office in Michael Reese Hospital. Officers of the organization are: Paul D. White, M.D., Boston, President; John Palmer, M.D., Montreal, Ignacio Chavez, M.D., Mexico City and D. Evan Bedford, M.D., London, Vice Presidents; Louis N. Katz, M.D., Chicago, Treasurer; Pierre W. Duchosal, M.D., Geneva, Secretary; Mrs. Margaret Stern, Michael Reese Hospital, Chicago, Assistant Secretary; and Frank D. Mayer, Chicago, Board Member. In addition to Drs. White, Chavez and Duchosal, the Advisory Committee members are: E. Braun-Menéndez, M.D., Buenos Aires; Paul Wood, M.D., London; Jean Lenegre, M.D., Paris; and Mariano Alimurung, M.D., Manila, P. I.

PULMONARY FUNCTION COURSE SCHEDULED FOR PHYSICIANS

A course for physicians interested in diseases of the chest who wish to become acquainted with methods used in the evaluation of pulmonary function and related cardiac function will again be presented at Boston City Hospital, March 24-28, it was announced by the American Trudeau Society. Tuition for the course, which includes demonstrations, is $75. Application blanks and detailed information may be obtained from Edward J.

Welch, M.D., 1101 Beacon Street, Brookline 16, Mass.

AHA-NBC PRESENT TV SERIES TO INTEREST YOUNG PEOPLE IN RESEARCH CAREERS

A series of television programs designed to interest high school and college students in careers as research investigators in the medical and biological sciences will be presented by NBC-TV and the Heart Association, in cooperation with the Educational Television and Radio Center, for 13 weeks beginning March 24. Assisted by a grant from E. R. Squibb and Sons, a division of Olin Mathieson Chemical Corporation, the "live" half-hour programs will be shown over most stations of the Educational Television network on Mondays at 6 p.m. EST. In addition, some NBC-TV stations will carry the live programs.

The series, first of its kind designed to help fill the need for capable young people in medical research, will present to the viewer the nature of investigative work and the stimulating world which it represents. Various areas of research in the medical and biological field will be discussed each week by leading cardiovascular investigators. The background of an important research problem will be documented from its early history to its present status.

The entire series will be kinescoped for later showings on regular network stations and on additional stations of the Educational Television network. Local Heart Associations will show the kinescopes at classes and science clubs and in connection with their Health Careers programs.

MEETINGS CALENDAR

March 20-22: Chicago Heart Association, Conference on Pulmonary Circulation, Chicago. Wright Adams, M.D., Department of Medicine, University of Chicago, Chicago, Ill.

March 24-27: American Academy of General Practice, 19th Annual Scientific Assembly, Dallas. Mac F. Cahal, Volker Blvd. at Brookside, Kansas City 12, Mo.

April 16-18: American Surgical Association, New York. R. K. Gilchrist, 59 E. Madison Street, Chicago 3, Ill.

April 24-26: Fifth International Congress of Internal Medicine, Philadelphia. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

April 28-May 2: American College of Physicians, Atlantic City. E. R. Loveland, 4200 Pine Street, Philadelphia 4, Pa.

May 4: American Federation for Clinical Research, Atlantic City. William W. Stead, VA Hospital, Minneapolis 17, Minn.

May 5: American Society for Clinical Investigation, Atlantic City. S. J. Farber, 550 First Ave., New York 16, N. Y.

May 6-7: Association of American Physicians, Atlantic City. P. R. Beeson, Yale University School of Medicine, New Haven 11, Conn.

May 8-9: American Pediatric Society, Atlantic City. A. C. McGuinness, 2800 Quebec Street, N.W., Washington 8, D. C.

June 23-27: American Medical Association, San Francisco. George F. Lull, 535 N. Dearborn, Chicago 10, Ill.

ABROAD

April 16-19: International Academy of Legal Medicine and Social Medicine, 50th International Congress, Madrid. Prof. B. Piga, Professor of Legal Medicine, Madrid University, Madrid, Spain.

September 14-21: Third World Congress of Cardiology, Brussels. Dr. F. Van Dooren, 80 Rue Merceiis, Brussels, Belgium.

THIRD WORLD CONGRESS OF CARDIOLOGY
Brussels, September 14-21, 1958
IMPORTANT REMINDER

The officers of the Third World Congress of Cardiology wish to remind all physicians who plan to attend the Congress that registration blanks and fees should be forwarded as soon as possible.

The deadline for registration is set definitely for May 1, 1958

Information about the Congress, particularly about registration and blanks for hotel accommodations, may be obtained from the American Heart Association, 44 East 23rd Street, New York 10, N.Y.

For special information other than registration and blanks it will be necessary to write directly to: Dr. Fr. Van Dooren, 80 rue Merceiis, Brussels, Belgium.

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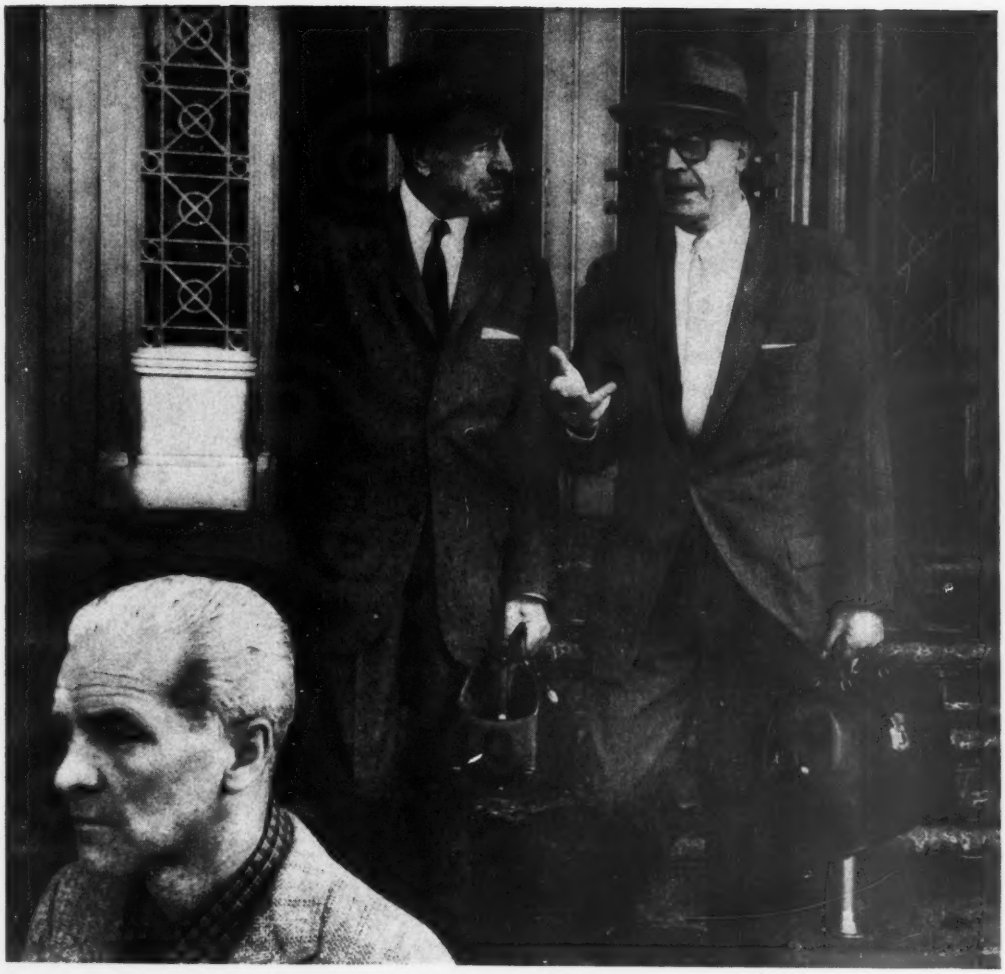

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